MAR 19 1935

VOLUME 5 MARCH, 1935 NUMBER 2

MEDICAL LIBRARY

American Journal of Clinical Pathology

OFFICIAL PUBLICATION
THE AMERICAN SOCIETY OF CLINICAL PATHOLOGISTS

CONTENTS

Pathology of Oil Aspiration Pneumonia (Lipoid Pneumonia). KANO IKEDA... 89
The Thyroid Gland in Kansas. C. ALEXANDER HELLWIG..... 103
Epidermoid Carcinoma of Lung and Pleura vs. Endothelioma of Pleura. A Case Report. THOMAS M. PEERY AND KENNETH M. LYNCH..... 112
Adrenal Disease in Relationship to Hypoglycemia and Death. JACK C. NORRIS..... 120
A Postmortem Analysis as to Etiology in One Thousand Cases of Peritonitis. C. C. PFLAUM..... 131
Paroxysmal "March" Haemoglobinuria with a Report of a Case. E. M. WATSON AND L. C. FISCHER..... 151
A Very Rapid Flocculation Method for the Diagnosis of Syphilis. A Preliminary Report. F. RYTZ..... 159
Studies in Cerebrospinal Fluid. II. BENJAMIN GRUSKIN..... 162
Technic for Preservation and Microscopic Demonstration of Nodules in Gout. ELENA DE GALANTHA..... 165
Editorial..... 167
News and Notices..... 171

PUBLISHED BI-MONTHLY BY THE WILLIAMS & WILKINS COMPANY
MOUNT ROYAL AND GUILFORD AVES., BALTIMORE, U. S. A.
Made in United States of America

American Journal of Clinical Pathology

EDITOR

T. B. MAGATH, Mayo Clinic, Rochester, Minnesota

ADVISORY EDITORIAL BOARD

C. S. BUTLER, U. S. Naval Hospital, Brooklyn, N. Y.

H. J. CORPER, National Jewish Hospital, Denver, Colo.

B. C. CROWELL, American College of Surgeons, Chicago, Ill.

HERBERT FOX, Pepper Laboratory of Clinical Medicine, University of Pennsylvania, Phila., Pa.

A. S. GIORDANO, 531 North Main Street, South Bend, Indiana

F. W. HARTMAN, Henry Ford Hospital, Detroit, Mich.

R. A. KILDUFFE, Atlantic City Hospital, Atlantic City, N. J.

J. A. KOLMER, Temple University School of Medicine, Philadelphia, Pa.

S. P. REIMANN, Lankenau Hospital, Phila., Pa.

A. H. SANFORD, Mayo Clinic, Rochester, Minnesota

WALTER M. SIMPSON, Miami Valley Hospital, Dayton, Ohio

W. S. THOMAS, Clifton Springs Sanatorium, Clifton Springs, N. Y.

WARREN T. VAUGHAN, 808 Professional Bldg., Richmond, Va.

American Society of Clinical Pathologists

OFFICERS

President, F. H. LAMB, Davenport, Iowa

Vice-President, B. S. KLINE, Cleveland, Ohio

President-elect, F. M. JOHNS, New Orleans, Louisiana

Secretary-Treasurer, A. S. GIORDANO, South Bend, Indiana

STANDING COMMITTEES

EXECUTIVE COMMITTEE

A. G. FOORD, Chairman, Pasadena, California

KANO IKEDA, St. Paul, Minnesota

W. M. SIMPSON, Dayton, Ohio

H. C. SWEANY, Chicago, Illinois

H. J. CORPER, Denver, Colorado

C. I. OWEN, Detroit, Michigan

BOARD OF CENSORS

C. W. MAYNARD, Chairman, Pueblo, Colorado

S. P. REIMANN, Philadelphia, Pennsylvania

H. A. HEISE, Milwaukee, Wisconsin

A. V. ST. GEORGE, New York, N. Y.

W. S. THOMAS, Clifton Springs, New York

A. H. BRADEN, Houston, Texas

BOARD OF REGISTRY

PHILIP HILLKOWITZ, Chairman, Denver, Colorado

W. E. KING, Detroit, Michigan

ASHER YAGUDA, Newark, New Jersey

R. R. KRACKE, Emory University, Georgia

H. H. FOSKETT, Portland, Oregon

KANO IKEDA, St. Paul, Minnesota

Entered as second-class matter, January 7, 1931, at the Post Office at Baltimore, Md., under the act of March 3, 1879

Copyright 1935, The Williams & Wilkins Company

PATHOLOGY OF OIL ASPIRATION PNEUMONIA (LIPOID PNEUMONIA)*

KANO IKEDA

From the Pathological Laboratory of the Chas. T. Miller Hospital, Inc., Saint Paul, and the Department of Pathology, University of Minnesota, Minneapolis

A peculiar pneumonia resulting from the accidental aspiration of oils and fats has been recorded only on rare occasions and frequently escapes the observation in routine clinical and pathologic examination. A relatively benign and usually localized, proliferative type of inflammation of chronic tendency, is usually observed among debilitated infants and often found in association with terminal acute septic pneumonia. It is also encountered, occasionally, in older children and adults, usually in more chronic form.

For the sake of simplicity and to avoid possible confusion as to its etiology and pathogenesis, the term "oil aspiration pneumonia" has been applied to designate the condition in preference to "lipoid pneumonia."

INCIDENCE

The incidence of oil aspiration pneumonia is difficult to estimate. Since 1925, eighteen cases have been reported by four American authors.[6, 9, 10, 12] Fourteen of these occurred in infants less than 30 months old, three between the ages of three and six and one in an adult 37 years of age. Recently, two additional cases were reported in Germany,[1, 3] both in adults, more than 50 years of age. Holt[5] collected twenty-three cases of "lipoid pneumonia" in seven years and fourteen of these were in infants under two years of age. In 1927, Pinkerton[10] collected six cases in 290

* Read before the Thirteenth Annual Convention of the American Society of Clinical Pathologists, Cleveland, Ohio, June 8 to 11, 1934.

consecutive necropsies. From a series of 101 consecutive post mortem examinations on children, in three years I was able to collect seven cases of this type of pneumonia, five of them occurring in babies less than twelve months old. In the original necropsy protocol of these cases, a diagnosis of oil aspiration pneumonia was not recorded since the condition was not recognized at the time of necropsy. This, in a general way, is in keeping with the experience of others. Recently, however, a typical case of chronic oil aspiration pneumonia was recognized accidentally in an adult woman,[8] the only one out of several thousands of necropsies on adults in the past several years.

ETIOLOGY

Oil aspiration pneumonia occurs rarely in healthy individuals. Accidental aspiration of oil may occur, most frequently, among debilitated infants during physical struggle against forced administration of oily substances. This appears to be the principal cause of aspiration in babies since most of them are fed artificially and are subject to vomiting, regurgitation, choking or gagging on feeding. Instillation of oil into the nose is also considered of etiologic importance, since many are prone to upper respiratory infection, for which nasal instillation of oil is routinely practiced. The oil so instilled finds its passage into the trachea without causing conscious reflex inhibition. Certain mechanical and neurogenic factors which interfere with normal function of swallowing may also contribute to aspiration. This is particularly important in older individuals.

The oils most commonly encountered in this type of aspiration pneumonia are (1) mineral oil and its various combinations, used as nasal drops and inhalants and also as laxatives and (2) cod liver oil (haliver oil). These oils apparently cause more lasting and profound reaction in the pulmonary parenchyma than any other oils in actual use. Milk and cream appear less harmful, although the simultaneous introduction of a large number of micro-organisms may cause localized suppurative pneumonitis. Castor oil, olive oil and poppy seed oil (lipiodol) cause the least of reaction in the lung and appear to be eliminated with relative

ease, although by no means entirely free from harmful effects on the pulmonary parenchyma. More than one kind of oil may be aspirated in the course of long protracted illness.

PATHOLOGY

Grossly, the lung presents an appearance of bronchopneumonia. Close observation, however, may elicit certain atypical features. The lung is not only lumpy on palpation but rubbery in consistency. Yellowish mottling of the pleural surfaces may be conspicuous. The cut surface is usually dry and may show irregular areas of yellowish or orange-yellow peribroncheal consolidation, usually sharply outlined against, but sometimes merging gradually into, the surrounding meaty parenchyma. Bronchopneumonic patches are usually more grayish while small abscesses are whiter than the typical lesion of oil pneumonia. Areas of fibrosis may be recognzed. Oily fluid may exude from the cut surface. Pus is expressed only in the presence of bronchopneumonia or purulent bronchitis. Yellowish, circumscribed, nodular lesions, simulating tumor growths may be encountered in chronic cases. Microscopically, the fundamental pathologic process is essentially that of a foreign body reaction in the presence of insoluble oil and consists primarily of (1) the massive infiltration of macrophages, (2) the proliferation of stromal cells, and (3) the appearance of foreign body giant cells. The macrophages and giant cells usually contain droplets of oil. Globules of free oil are found deposited within distorted alveolar spaces and in the intervening pneumonic areas. In chronic cases, well localized granulomatous lesions may develop around the entrapped masses of oil. The degree of fibrosis is, on the whole, proportionate to the duration of the lesion. The picture may become, more or less modified by the secondary exudative process due to chemical irritants or bacterial activity.

REVIEW OF EXPERIMENTAL WORK

The specific changes which may take place in the lung as a result of the intratracheal injection of oily preparations were not recorded either by Rosenberg[13] who, as early as 1885, reported

the use of this procedure in the treatment of certain chronic pulmonary diseases, or by those who employed this method of treatment. In 1917, Winter and his co-workers[14] published their observations with the experimental introduction of iodoform—olive oil mixture into the trachea of dogs. They saw a possible means of treating certain pulmonary lesions and at the same time, of obtaining diagnostic roentgenograms of the chest. In 1920, a study on the effects of olive oil introduced into the lungs of animals was made by Guieysse-Pellissier.[4] Corper and Fried[2] studied the changes in the lungs of animals following the intratracheal administration of chaulmoogra oil, paraffin oil and olive oil. All of these investigators concluded that the introduction of these oils into the trachea produced a proliferative type of inflammation of the lung, in varying intensity. Following the observation at necropsy of cases of "pneumonia following naso-pharyngeal injections of oils," Laughlen[1] undertook simple animal experimentation by the intratracheal and intra-oral administration of menthol alboline mixture and reproduced the pulmonary lesion, found in man at necropsy. Pinkerton[10,11] made a thorough and comprehensive investigation of this type of pneumonia in six necropsied cases and in a large number of animals, killed or which died at varying intervals, following the intratracheal injection of mineral oil and various animal and vegetable oils in common use. He concluded that the intensity and the type of pneumonia produced depended upon the kind of oil employed. On the whole, vegetable oils, with a notable exception of chaulmoogra oil, were inert and harmless; mineral oil was not hydrolysed, behaved as a foreign body and caused active proliferative reaction and phagocytosis; animal oils were partly hydrolysed, often causing exudative inflammation and resulting fibrosis through liberation of free fatty acids and partly act as a foreign body either in free state or as an insoluble oxidation product, stimulating fibrosis and production of giant cells. He called attention to a peculiar proliferative activity of the epithelium with the use of lard oil which he characterized as "neoplastic activity." This is of interest in view of the similar results I was able to obtain with other animal oils and certain medicated oils. Pinkerton also endeavored to differ-

entiate various oils in the tissue by special staining methods which may be employed successfully in selected cases.

REPORT OF ANIMAL EXPERIMENTS

The results of my work, thus far obtained, with a large number of rabbits, subjected to the intratracheal instillation of such oils as chaulmoogra oil, olive oil, lipiodol, castor oil, cream, cod liver oil, haliver oil, rabbit fat oil, lard, mineral oil, mixture of menthol, oil of eucalyptus and alboline, ephedrine inhalant, metaphedrine,

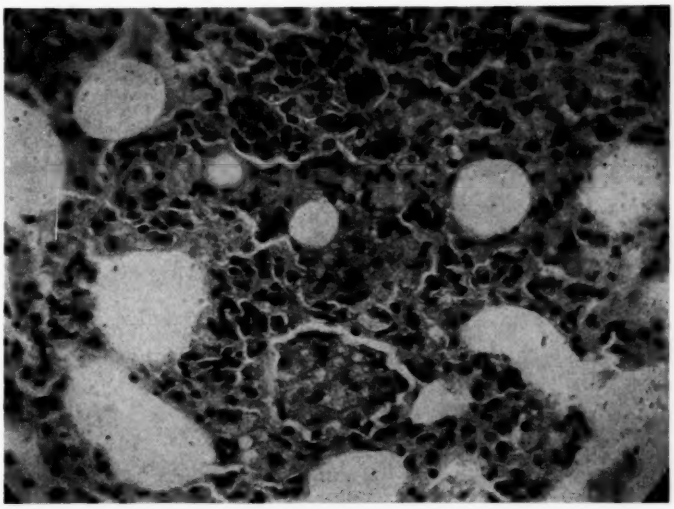


FIG. 1. A NODULAR AREA OF PROLIFERATIVE PNEUMONITIS AROUND OIL MASSES, TWO AND A HALF WEEKS AFTER THE INTRATRACHEAL INJECTION OF 3 CC. LIPIODOL IN RABBIT

viosterol, et cetera and killed or which died at varying intervals, showed little essential difference from those reported by Pinkerton. Detailed account of this work will be presented in a future communication. A few cardinal observations of practical significance will be briefly noted at this time.

The immediate local effects of the aspirated oil on the pulmonary parenchyma were those of mechanical obstruction to a group or groups of alveoli due to their temporary occlusion by the oil. There were localized hemorrhages and edema which soon

subsided with partial elimination of the foreign oil. If the amount of oil proved sufficiently large or the oil too irritating, death usually resulted from massive hemorrhage and edema which extended into large portions of the lungs.

Vegetable oils were, as a rule, the least irritating and provoked less tissue reaction than oils of either the animal or mineral origin. However, it was consistently found that such vegetable oils as were employed, namely, castor oil, olive oil and lipiodol, all showed a slight degree of proliferative reaction and the invasion of macrophages in small numbers about the retained oil drops. This, at least, suggests a possibility of like changes in the human lung following the introduction of these oils (figure 1). Chaulmoogra oil, which was once suggested[7] in the treatment of tuberculous laryngitis, was found to be extremely damaging to the pulmonary parenchyma, minute quantities of the oil causing intense hemorrhagic exudation and diffuse edema. This was attributed by Pinkerton and Corper to the high free fatty acid value of the oil. For the same reason, olive oil was also found to be irritating to the lung; however, in a far less degree.

Animal oils are known to undergo hydrolysis in the lung. Masses of the free oil in the pneumonic area showed an irregular staining reaction and shreddy disintegration which was interpreted to indicate certain chemical changes. There was apparently gradual absorption of the digested oil through diffusion. Unhydrolysed oil was partly phagocytized by macrophages which not only transported it to the regional lymphatic capillaries for disposal but apparently caused its digestion through an intracellular lipolytic enzyme, as was suggested by the varied staining reaction shown by the oil droplets within the same cells. Of the animal oils, cold liver oil was most damaging to the pulmonary tissue. It immediately provoked intense fibrinous exudation coupled with local edema, congestion and leukocytic infiltration. Within two weeks, it showed a greater tendency, than other animal oils, to cause proliferative activity of the lining epithelium of the terminal broncheols, which spread rapidly along the adjacent alveolar linings and epithelialized them with a layer of large cuboid or columnar cells (figure 2). Still later, however, the oil

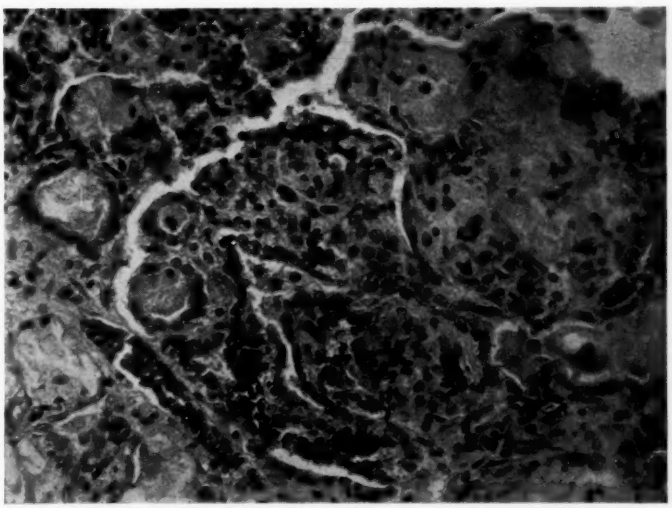


FIG. 2. BEHAVIOR OF THE ALVEOLAR EPITHELIUM AROUND COD LIVER OIL WHICH FILLS THE ALVEOLAR SPACES

The oil is partly oxidized and insoluble. Fourteen days after intratracheal injection.

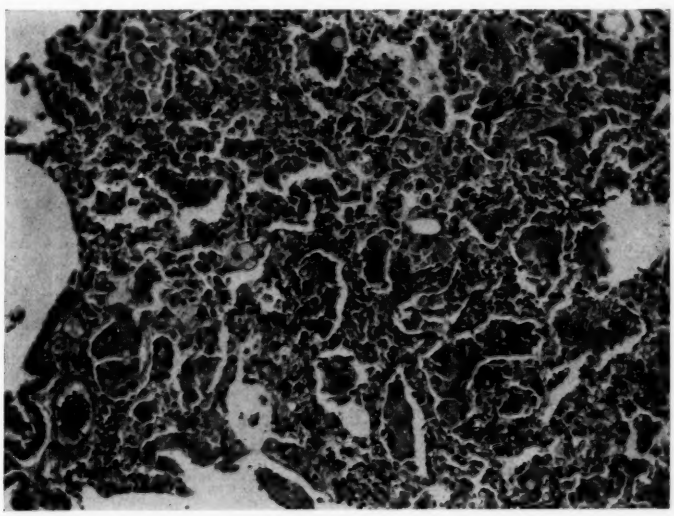


FIG. 3. FOREIGN BODY GIANT CELLS IN LARGE NUMBERS AROUND OXIDIZED INSOLUBLE MASSES OF COD LIVER OIL

Forty-six days after intratracheal injection of 4 cc. of cod liver oil

became transformed, through oxidation, into an inert insoluble foreign body which stimulated the formation of giant cells, but apparently lost its irritant effect on the epithelium (figure 3).

Mineral oil did not show any histologic evidence of hydrolysis. Its behavior was, in every respect, that of a foreign body. It was freely phagocytized by macrophages which poured into the involved areas. The oil appeared to be emulsified in the process of phagocytosis. Masses of the oil laden macrophages caused the

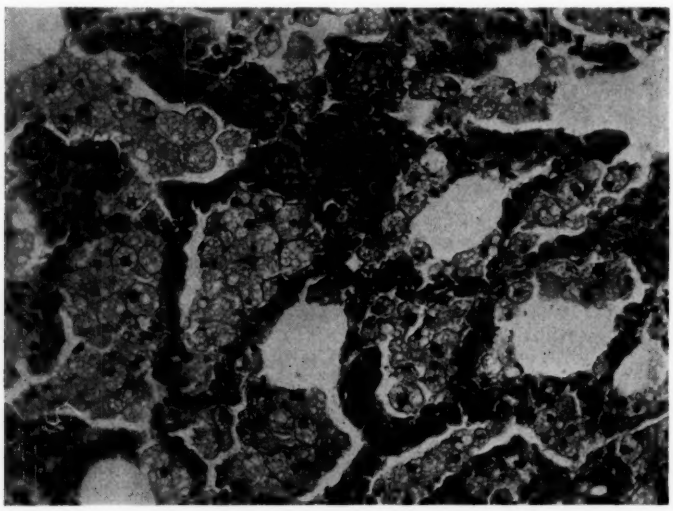


FIG. 4. MACROPHAGES DISTENDED WITH EMULSIFIED MINERAL OIL, FILLING THE ALVEOLAR SPACES

Fifty days after injection

obliteration of many alveoli. Many of these cells were, undoubtedly, eliminated either through expectoration or through the regional lymphatic channels but many others remained for many weeks entrapped within alveolar spaces (figure 4). Proprietary preparations for nasal instillation containing such drugs as ephedrine, camphor, et cetera dissolved in mineral oil were found to cause certain changes in the pulmonary parenchyma which were apparently due to the combined effects of the drug and the mineral oil. These changes were characterized by the

active proliferation of the broncheolar epithelium with epithelialization of the alveolar linings (which was undoubtedly brought about by the drug) and the massive collection of oil laden macrophages within involved alveoli. Diffuse interstitial fibrosis with the appearance of foreign body giant cells and deposition of calcium were observed in the lungs subjected to instillation of a plain ephedrine inhalant (figure 5). These striking pictures were

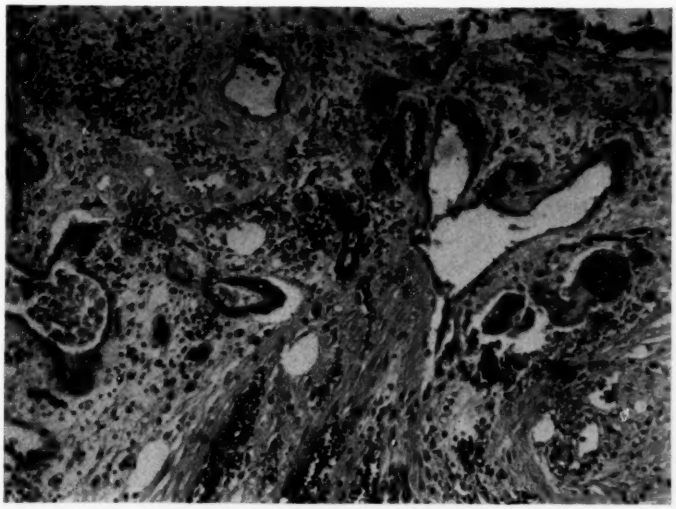


FIG. 5. DIFFUSE FIBROSIS WITH AREAS OF ROUND CELL INFILTRATION; DISTORTED ALVEOLI LINED WITH CUBOID EPITHELIUM; SEVERAL FOREIGN BODY GIANT CELLS; OIL LADEN MACROPHAGES IN ALVEOLAR SPACES AND SCATTERED ABOUT IN THE FIELD; AND FEW CALCIUM DEPOSITS, 31 DAYS AFTER INJECTION OF EPHEDRINE INHALANT

produced in animals only through the use of proprietary mineral oil preparations and simulated the changes which might be obtained in the lung through the simultaneous instillation of cod liver oil and mineral oil.

DISCUSSION OF PUBLISHED CASES

Twenty cases which may be properly classed as "oil aspiration pneumonia" have been reviewed from the literature. Fourteen of the twenty occurred in young infants in whom the clinical

picture was fairly identical though differing somewhat in its course; the etiologic factors were more or less constant and the cause of death was invariably a teriminal sepsis and bronchopneumonia. Of the remaining six cases, three were in adults and three in children between three and six years of age. The aspiration in these six patients was not a mere accident as in the fourteen infants but was made practically inevitable by certain contributing factors such as the paralysis of the accessory laryngeal muscles, direct intralaryngeal instillation, diabetic stupor, and other conditions. The clinical course of the cases in this group was generally prolonged, with a possible exception of one, a child of three who was suffering from diabetes.[6]

At necropsy, death was attributed to bronchopneumonia with or without general sepsis in eighteen of the twenty cases. One was a clinical case with a diagnosis of chronic pulmonary cirrhosis, related to the aspiration of oil, when reported.[1] The other case died apparently of cardiac failure due to chronic pulmonary fibrosis.[3] All of the cases examined at necropsy showed the presence of oil laden macrophages and droplets of free oil in the pneumonic area. In a few instances, the presence of giant cells and fibrosis was noted while in three cases with a prolonged clinical course there were circumscribed nodular areas scattered in the lungs due to chronic granulomatous inflammation and localized fibrosis.

REVIEW OF AUTHOR'S CASES

An analysis of the seven cases of my series of children revealed a cleft-palate and hare-lip to be a contributing factor in aspiration in two instances and a central or local interference with deglutition in three others. All seven received artificial feeding a greater part of their lives. Six children had a history of recurring upper respiratory infection and at least five had purulent nasal discharge. Four patients were given instillation of nasal oil; four were fed cod liver oil, one, haliver oil and one viosterol. Five children showed clinical and necropsy evidence of acute septic pneumonia, in three of them this was evidently due to massive aspiration of feedings, while in two older infants, death was due

to acute post-operative aspiration and shock. There was antidating interstitial, proliferative pneumonia with infiltration of many oil laden macrophages in all seven cases while giant cells were present in six (figure 6). Globules of free oil were, more or less, conspicuous in the alveolar spaces and within the pneumonic areas.

Another case of oil aspiration pneumonia which came under observation within recent months occurred in an adult in whom no

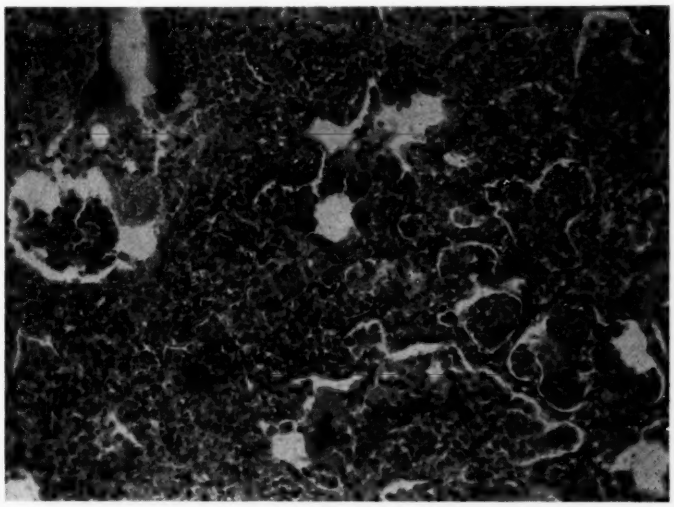


FIG. 6. CASE A-30-1621. A TYPICAL PNEUMONIC AREA SHOWING CLUMPS OF OIL LADEN MACROPHAGES IN ALVEOLAR SPACES, DIFFUSE PROLIFERATION OF SEPTAL CELLS, AND SEVERAL FOREIGN BODY GIANT CELLS

history could be elicited as to the possible administration of an oil during her protracted illness.

This was a female, aged 69 who complained of marked asthma, tremor and rigidity of the hands, arms, body and legs which began about four years ago.[8] For the past three months, the patient had great difficulty in swallowing and took little nourishment. At necropsy, there was hypostatic congestion in the dependent portions of both lungs. There was a well-defined, firm, rubbery, tumor-like area of consolidation, 5 cm. in diameter in

the lower lobe of the right lung. The cut surface of this mass showed areas of whitish, fibrous consolidation from which yellowish material was expressed. Microscopically, there was a diffuse connective tissue proliferation around globules of oil, obliterating alveolar spaces and showing areas of round cell infiltration and many oil laden macrophages and a few giant cells (figure 7). Both osmic acid and the Ciaccio's stains reacted negatively, indicating the oil concerned in the process to be mineral oil.

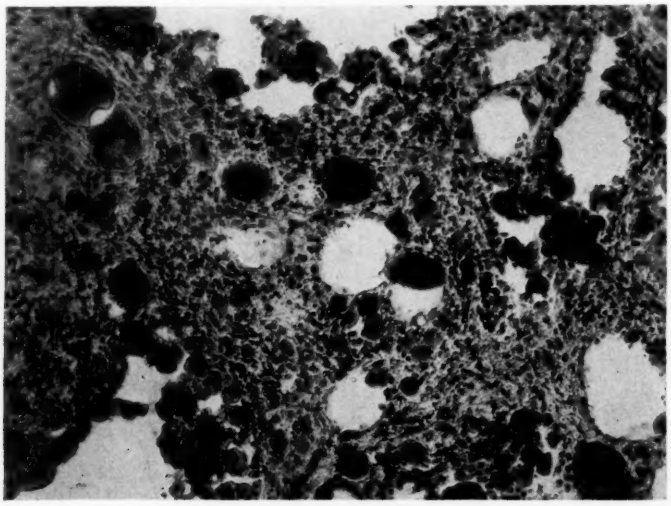


FIG. 7. CASE A-34-312. FROM A LESION IN ADULT CASE, STAINED WITH SCARLET R. SHOWING OIL GLOBULES IN REMNANT ALVEOLAR SPACES, OIL LADEN MACROPHAGES AND GIANT CELLS

A tumor-like lesion such as this represents an advanced stage of localized oil aspiration pneumonia, most likely to develop under prolonged presence of mineral oil within the pulmonary parenchyma, and may properly be viewed as a "paraffinoma."

The mere presence of free oil droplets in the pneumonic exudate which may occur in acute massive aspiration pneumonia does not justify a microscopic diagnosis of oil aspiration pneumonia. The oil droplets found in the former usually represent globules of milk in the feeding. Differential diagnosis is readily established

by noting the absence of the basic criteria of true oil aspiration pneumonia which have been discussed.

SUMMARY AND CONCLUSIONS

(1) A pneumonia, hitherto seldom described, which is believed to have an intimate etiologic relation with the accidental aspiration of oily substances, is termed oil aspiration pneumonia.

(2) The incidence, etiology and pathology of this condition are briefly given.

(3) Experimental work by contemporary investigators is referred to and the more important data obtained by the author's own animal experimentation are summarized.

(4) Cases reported in the recent literature and those of the author's series are briefly discussed.

(5) It may be concluded that:

(*a*) Oil aspiration pneumonia is a definite entity with fairly characteristic clinical syndrome and constant pathologic changes.

(*b*) Of the oils routinely used for either the nasal or the oral administration, cod liver oil (haliver oil), mineral oil and certain proprietary medicated mineral oils probably cause more permanent and severe reaction in the lungs of man as well as experimental animals than any other oils in routine use.

(*c*) Oil aspiration pneumonia is pre-eminently a disease of early infancy.

(*d*) It should be possible to make the diagnosis of this condition clinically and to recognize this type of pneumonia at necropsy with greater frequency and precision.

REFERENCES

(1) Bodmer, H., and Kallós, P.: Über schwere Lungenschädigung (Lungenzirrhose) infolge Aspiration von Paraffinöl bei Therapeutischer Anwendung. Arch. f. Ohren, Nasen u. Kehlkopfheilk., **136:** 40–45. 1933.

(2) Corper, H. J., and Freed, Harold: Intratracheal injection of oils for diagnostic and therapeutic purposes. Jour. Am. Med. Assn., **79:** 1739–1743. 1922.

(3) Fischer-Wasels, B.: Tödliche Lungenschrumpfung durch Gebrauch von Mentholöl. Frankf. Zeitschr. f. Path., **44:** 412–425. 1933.

(4) Guieysse-Pellissier, A.: Recherches sur l'absorption de l'huile dans le poumon. C. R. Soc. de biol., **83:** 809–811. 1920.

(5) Holt, L. E., and McIntosh, R.: Lipoid pneumonia. In Holt: Diseases of infancy and childhood, ed. 10. New York: Appleton and Company, pp. 464–466. 1933.

(6) Laughlen, G. H.: Studies on pneumonia following naso-pharyngeal injections of oil. Am. Jour. Path., **1:** 407–414. 1925.

(7) Lukens, R. M.: Chaulmoogra oil in the treatment of tuberculous laryngitis. Jour. Am. Med. Assn., **78:** 274–275. 1922.

(8) Necropsy Protocol, Department Pathology, University Minnesota, A-34-312. 1934.

(9) Pierson, J. W.: Some unusual pneumonias associated with the aspiration of fats and oils in the lungs. Am. Jour. Roentg., **27:** 572–579. 1932.

(10) Pinkerton, Henry: Oils and fats. Their entrance into and fate in the lungs of infants and children. Am. Jour. Dis. Child., **33:** 259–285. 1927.

(11) Pinkerton, Henry: The reaction to oils and fats in the lung. Arch. Path., **5:** 380–401. 1928.

(12) Rabinovitch, J., and Lederer, M.: Lipoid pneumonia. Arch. Path., **17:** 160–168. 1934.

(13) Rosenberg, A.: Zur Behandlung der Kehlkopf-und Lungen-Tuberculose. Berl. Klin. Wochenschr., **24:** 466–470. 1887.

(14) Waters, C. A., Bayne-Jones, S., and Rowntree, L. G.: Roentgenography of the lungs. Arch. Int. Med., **19:** 538–549. 1917.

THE THYROID GLAND IN KANSAS*†

C. ALEXANDER HELLWIG

From the Pathological Department, St. Francis Hospital, Wichita, Kansas

Since 1910 systematic comparative studies have been made on normal thyroids from different European regions. They have given much information on the anatomical basis and the earliest stages of endemic goiter. Most interesting results were obtained by workers in Switzerland[13] and in Germany.[3] It was demonstrated that the non-goitrous thyroids of the Swiss mountains differ widely in their histologic structure from the thyroids of the North German plains. The small size of the acini, scanty and thick colloid, poor blood supply and abundance of fibrous stroma are the characteristics of the normal thyroid gland in Switzerland.

There are available today morphologic data on the thyroids from most localities of Europe. In our country also, the interest in this field of geographic pathology is apparent from several comparative anatomic and chemical studies of the normal thyroid, for instance reports from Illinois by Jaffé,[7] from Minnesota by Rice[11] and from South Carolina by von Kolnitz and Remington.[8]

Besides elucidating the histogenesis of goiter, systematic studies of thyroids from different regions should also be of practical value for goiter surveys. The present statistics on the frequency and geographic distribution of goiter, based as they are on clinical examination of certain parts of the population, are unsatisfactory, because they do not consider all age groups. Necropsy studies furnish the only reliable information on the incidence of goiter in a given locality.

It is to be regretted that the comparative thyroid studies in

* Read before the Thirteenth Annual Convention of the American Society of Clinical Pathologists, Cleveland, Ohio, June 8 to 11, 1934.

† Aided by a grant from the Committee on Scientific Research of the American Medical Association.

this country do not follow a uniform plan. Jaffé who collected the data on 1000 thyroids obtained at necropsy in Chicago, considered only the weight and gross anatomy. Few will accept his contention that thyroids with nodules, even if the weight of the gland is normal, must be regarded as goiters. Rice, in his very complete paper, described the gross and microscopic structure of 493 thyroids obtained at necropsy. His data on the weight of the thyroids are, however, without value, because he does not accept a normal weight of the thyroid. Von Kolnitz and Remington determined, on 150 normal thyroids from South Carolina, only the weight and the iodine content.

My own material, collected in Wichita, cannot compare with the large numbers of Jaffé and Rice, as only little more than 100 thyroids were analysed. I hope that the lack of quantity is compensated by more detailed study. Of each thyroid, I determined not only weight and size of the two lobes, but I measured also the diameter of the acini with the micrometer eyepiece, noted the degree of epithelial proliferation and, finally, considered the number and size of nodules. By using these various criteria, I was able to compare my findings with the data available from European as well as from North American material.

THYROID WEIGHT

The average weight of the thyroid in necropsy material furnishes the most valuable information about presence or severity of endemic goiter in a given locality. In Wichita, I found the average weight of adult thyroids without nodules to be 23.2 grams, while Jaffé reported for the region of Chicago an average weight of 27.8 grams, Rice for Minnesota 23.2 grams and von Kolnitz 18.8 grams for Charleston. In a goiter-free North German region (Kiel) the average thyroid weighs 23 grams as compared with 39 grams in the center of the Swiss endemic region (Bern). The thyroid of the newborn, in North America, is very small. While Wegelin[14] gives the weight of the thyroid in newborns as 8.2 grams in Bern and as 1.9 grams in Kiel, the following figures were obtained in necropsy material of this country: Chicago 2.1 grams, Minneapolis 1.8 and Wichita 1.2 grams.

Considering the different periods of life, I observed the most rapid growth of the thyroid gland shortly before and during puberty, in both the males and the females. Between 16 and 20 years, the average weight in my series is 21.7 grams, the same as in Chicago, but decidedly higher than in Charleston (17.3 grams). In Wichita, glands without nodules reach a maximum weight during the fourth decade of life, namely 29.5 grams, which compares with the figures obtained in Chicago (30.8) and Minneapolis (30.6), but is almost 10 grams more than the average weight in Charleston. After the 40th year, the weight curve shows a continuous decline, until it drops at the age of 70 to 14.7 grams in Wichita, to 25.3 grams in Chicago and 10.5 grams in Charleston.

In goiter statistics, there is great confusion due to the different interpretations of the term goiter. Arndt[1], therefore, proposes to define goiter as a thyroid gland weighing more than 35 grams in the adult. In the newborn, the thyroid gland should not be larger than 3 grams. As long as the thyroid weighs less than 35 grams, one is not justified in diagnosing goiter, even if there are nodules present. If Arndt's definition is accepted, the North American statistics based on necropsy material do not list the occurrence of congenital goiter. In my series of adult cases, 18.4 per cent showed goiters, which resembles the incidence in North Germany (16.1 per cent) as compared with 78.4 per cent in Bern. In Wichita, only 10.5 per cent presented a weight more than 40 grams and 3.9 per cent more than 50 grams. Our highest weight observed was 110 grams, in a white female, 62 years old.

DIAMETER OF ACINI

In comparing thyroids of the same age groups, from goitrous and goiter-free regions, Isenschmidt,[6] Sanderson-Damberg,[12] Clerc[4] and Schaer[13] agreed that the glands of mountainous endemic regions were composed of much smaller acini than those of non-goitrous regions. There existed an inverse relationship between thyroid weight and size of the acini. Aschoff,[2] May[9] and Arndt were unable to confirm these observations; however their

thyroid material was not so heterogenous as that of the Swiss workers.

The difficulty of determining the average size of the acini in a given thyroid is obvious, because the diameter may vary considerably within the same gland. Following Schaer's method I entered the micrometer readings in one of three columns. When the thyroid was composed of acini of uniform size, this figure was noted in the first column. In glands where another size was also

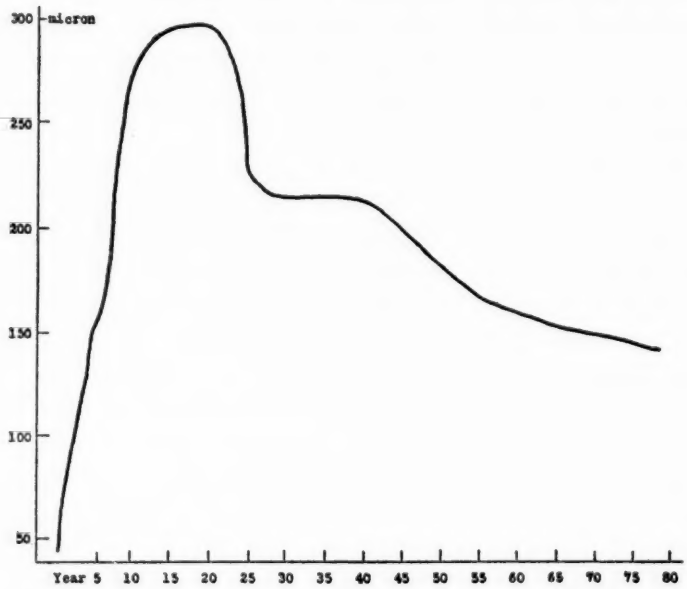


FIG. 1. THYROIDS OBTAINED AT NECROPSY IN KANSAS. AVERAGE SIZE OF ACINI, IN MICRONS, IN THE DIFFERENT AGE PERIODS

frequently encountered, this value was marked in the third row. Finally, when no single size was predominating and all acini varied between two extremes, these two limits were tabulated in the second row. Thus, it was possible to obtain the average diameter of each thyroid gland.

The curve in figure 1 illustrates the average size of the acini in the different age periods. At the time of birth the acini, in my material, are solid or had a very narrow lumen without colloid.

The size increases rapidly during the first years of life and as early as the fifth year amounts already to 150 microns. In my thyroids, the greatest increase in size of the follicles was noticed during puberty. The curve reaches its peak, with 300 microns, during the 23rd year of life. Then under fluctuations, it declines and we have as the average diameter in the 35th year, 220 microns, and in the 60th year 170 microns. The involution is concluded at the age of 85, with 150 microns.

In Minneapolis, where goiter is common, Rice obtained slightly lower figures. The maximum of his follicle curve, 250 microns, was observed in boys between 13 and 16 years, in girls three years later. After puberty, the size of the acini decreased continuously, dropped to 180 microns at sixty years and remained practically stationary throughout the remaining portion of life.

A comparison of the follicle curves of my series and of thyroids collected in other regions, demonstrates that the North American gland, even from a goiter-rich locality (Minneapolis), resembles the lowland type of Europe and has nothing in common with the thyroids of the Swiss goiter belt.

PROLIFERATIVE CHANGES

Sanderson-Damberg first described proliferative changes in normal thyroids. They consist of a cushion-like thickening of the acinar epithelium which becomes columnar and forms solid cell strands. The latter develop into small acini. The frequency and height of these proliferative areas are regarded as measure of increased thyroid activity. Most writers agree that they are more frequent in glands from goiter regions. May found that in Freiburg where endemic goiter is common, 27.3 per cent of thyroids obtained at necropsy show these cushion-like proliferations, in Northern Germany only 13.4 per cent. In Japan, there is epithelial proliferation in only 10 per cent of adult thyroids (de Oca)[10] and Arndt reported the lowest incidence, 3 per cent, in glands, obtained by necropsy from a goiter-free Russian locality. Since in our own material only 15.8 per cent of the glands had proliferative areas, the goitrogenic factor in our region is apparently as mild as in Northern Europe.

NODULES

According to Aschoff, it is not the incidence, but only the size of nodules in thyroids which distinguishes goitrous and goiter-free regions. He believes that the presence of small nodules is no evidence of endemic goiter. Since, however, de Oca demonstrated that in a really goiter-free country (Japan) nodules are entirely absent in thyroids obtained at necropsy, one is forced to believe that the presence of nodules in necropsy material indicates the activity of a goitrogenic agent. The nodules remain of small size in goiter-poor regions, probably because the food contains enough iodine to neutralize more or less the goiter-producing factor. Among my thyroids, there were 38.2 per cent containing nodules. Of these, 36.7 per cent were in males and 40 per cent in females. The frequency of nodules was more prevalent as age advanced. In adults, the incidence was 51.3 per cent. The youngest person presenting a nodule in my series, was a white boy, aged 15, with a thyroid weighing 24 grams. Of the glands containing nodules, 47.2 per cent had only one nodule, and there was no case exhibiting more than 6 nodules. Most of the nodules were small, only 14 per cent reached a diameter above 10 mm., and 71.4 per cent were less than 3 mm. in diameter. Microscopic study revealed that most of the nodules were composed of large acini, distended with thick colloid and only 5 per cent were parenchymatous.

Rice found that in Minneapolis 47.4 per cent of the necropsy cases presented nodules in the thyroid. The occurrence of nodules under 10 years of age was unusual, and there was a rapid rise in the incidence during early adult life. According to Jaffé's statistics, the frequency of nodules is less in Chicago, namely 30 per cent in males and 44.7 per cent in females. Also in this region, the size of the nodules is small, varying mostly between 5 and 20 mm.

The incidence of nodules in thyroids, the time of their development and their size characterize the regions of Chicago, Minneapolis and Wichita as lowlands from the standpoint of geographic pathology. My figures resemble the data collected on thyroid material of Northern Europe and are in contrast to the

conditions found in the Alpine endemic regions. In Goettingen of Northern Germany, 47 per cent of the glands at necropsy have nodules, in Bern 79 per cent.

COMMENT

My observations in Kansas are in accord, in many respects, with the findings of thyroids from other parts of North America; this seems to indicate that the differences in the structure and size of the North American thyroid from various localities are more of degree than of kind, in contradistinction to the wide differences observed in European glands. Nowhere, in this country, does apparently the normal thyroid present the characteristics as found in the mountainous regions of Switzerland. On the contrary, the early distention of the acini, during the first years of life, the richness in colloid characterize the North American thyroid as a lowland type as it is found in the plains of Northern Europe. With the North European thyroid, our glands have in common also the low average weight, the late appearance and the smallness of nodules.

On the other hand, the fact that after the 20th year of life, 18.4 per cent of our thyroids weighed more than 35 grams which is regarded as the upper limit of normal thyroids, and the observation that of our adult glands, 51.3 per cent presented one or several nodules, suggest that even in such a goiter-poor state as Kansas a goitrogenic agent is at work.

Studies of endemic goiter[5] have shown that in the center of mountainous goiter regions, as in Switzerland or the Himalayas, the parenchymatous goiters with small acini and scanty colloid are the most common structures of endemic goiter, while in level regions, as in Northern Europe or North America, the predominating type is the colloid goiter. These colloid-rich goiters of the lowland are closely related to hyperthyroidism, because exophthalmic goiter and other forms of thyrotoxicosis occur in just those localities where colloid goiter is most common. The colloid-poor goiter of the mountains, on the other hand, is more often associated with symptoms of deficient thyroid function.

Just as the goiters of different localities vary in their structure,

so do the non-goitrous glands. Just as the goiters of this country have nothing in common with the colloid-poor, parenchymatous type of endemic goiter as found in the Swiss Alpine regions, so also is the normal thyroid of our country a typical lowland gland and resembles closely the thyroids as found in the plains of Northern Europe.

CONCLUSIONS

The average weight of the thyroid gland in the region of Wichita, Kansas, is 23.2 grams for adults and 1.2 grams for the newborn.

18.4 per cent of thyroids from adults weigh more than 35 grams.

The diameter of the acini in this thyroid material is relatively large and the colloid content is high.

15.8 per cent of adult thyroids present proliferative changes in the acinar epithelium and 51.3 per cent have circumscribed nodules.

My observations on thyroids collected in Wichita, do not differ markedly from those made in Chicago and Minneapolis.

The North American thyroid gland resembles in size and structure the lowland type as found in the plains of Northern Europe.

Necropsy studies on thyroids furnish the only reliable information about the incidence of goiter in a given locality.

REFERENCES

(1) ARNDT, H. J.: Der Kropf in Russland. Jena: G. Fischer, 1931, pp. 282.

(2) ASCHOFF, L.: Report of the international conference on goiter in Berne (1927). Berne: Hans Huber, 1929.

(3) BÜCHNER, F.: Die Lebenskurve der Tieflandschilddrüse. Arch. f. klin. Chir., **130:** 199–206. 1924.

(4) CLERC, E.: Die Schilddrüse in hohen Alter vom 50. Lebensjahr an. Frankf. Zeitschr. f. Pathol., **10:** 1–19. 1912.

(5) HELLWIG, C. A.: Form und Funktion des nordamerikanischen Kropfes. Arch. f. klin. Chir., **154:** 1–31. 1929.

(6) ISENSCHMID, ROBERT: Zur Kenntnis der menschlichen Schilddrüse im Kindesalter. Frankf. Zeitschr. f. Pathol., **5:** 205–254. 1910.

(7) JAFFÉ, R. H.: The variation in weight of the thyroid gland and the frequency of its abnormal enlargement in the region of Chicago. Arch. Path., **10:** 887–894. 1930.

(8) VON KOLNITZ, H., AND REMINGTON, R. E.: Chemical studies on 150 normal human thyroids from Charleston, S. C. Endocrin., **17:** 563–568. 1930.

(9) MAY, H.: Zur Kenntnis der Lebenskurve der Schilddrüse im Kropfland und in kropffreier Gegend. Arch. f. klin. Chir., **149:** 501–509. 1928.

(10) DE OCA, MONTEZ: Das histologische Bild der japanischen Schilddrüse als Norm. Beitr. z. path. Anat. u. z. allg. Path., **85:** 333–348. 1930.

(11) RICE, C. O.: The life cicle of the thyroid gland in Minnesota. Western Jour. Surg. Obst., Gyn., **39:** 925–940. 1931.

(12) SANDERSON-DAMBERG, E.: Die Schilddrüsen vom 15. bis 25. Lebensjahr. Frankf. Zeitschr. f. Pathol., **6:** 312–334. 1911.

(13) SCHAER, H.: Vergleichende Untersuchungen an Schilddrüsen zwischen dem 25. und 50. Lebensjahr. Frankf. Zeitschr. f. Path., **36:** 249–274. 1928.

(14) WEGELIN, C.: Schilddrüse. In HENKE, F. AND LUBARSCH, O.: Handbuch der Speziellen Pathologischen Anatomie und Histologie. Berlin: J. Springer, **8:** 1–547. 1926.

EPIDERMOID CARCINOMA OF LUNG AND PLEURA VS. ENDOTHELIOMA OF PLEURA

A Case Report

THOMAS M. PEERY AND KENNETH M. LYNCH

From the Department of Pathology, Medical College of the State of South Carolina, Charleston, South Carolina

For many years the nature of "primary endothelioma of the pleura" has been a question among pathologists. The literature contains many reports of cases so diagnosed, but a careful study of these cases frequently leaves the impression that their nature is not unquestionable. One may suspect, also, that the nodules frequently described in the lung parenchyma, and assumed to be metastases from the pleural growth, may have been the primary neoplasms. Some writers are so bold as to report cases with this diagnosis from roentgen ray studies alone, or in conjunction with a punch biopsy.

Many of the writers admit the apparent epithelial nature of the tumor. Zeckwer[5] believes that such tumors

> have arisen from a multipotential cell which has differentiated now in one way, toward the epithelial type, now in another way, toward the fibroblastic, due to the fact that the mesothelial cells, in undergoing a neoplastic process, have reverted to a more embryonal type and have the potentialities of embryonal mesoblastic cells in differentiating in more ways then one.

He admits, however, that "a change in cell morphology is commonly seen in various tumors known to arise from a single type of cell."

Ewing,[1] while admitting difficulties in some cases, is inclined to believe that primary endotheliomata do occur, and derives them from the endothelial cells of the lymph spaces or from the lining cells of the pleural surface.

Harris,[2] reported a case of a similar type of tumor of the pleura in which

> the thickening was caused by an epithelial new-growth presenting all the features of squamous epithelioma, forming cell nests of an exactly similar appearance to what we find in the squamous epitheliomata of the lip.

He concludes:

> It must be admitted, however, as some will maintain, that such a growth is only apparently primary in the pleura, that although the pleura is the only part involved, and although careful examination of the subjacent lung showed the absence of any discoverable malignant disease, yet it is possible that the disease took its origin at some one minute spot in the lung and extended to the pleura, and that there the growth found the conditions most suited to its further development.

Robertson,[4] gave a critical review of the literature on the subject, and came to the conclusion that all pleural tumors except sarcomas are metastatic from neoplasms in some other part of the body, usually primary pulmonary neoplasms.

In view of the differences of opinion on the subject, it seems worth while to record a case which was tentatively diagnosed at necropsy as primary endothelioma of the pleura with metastases to peribronchial and cervical lymph nodes and to the peritoneum, this diagnosis being largely by reason of failure to find the primary neoplasm at the time. No definite parenchymal nodules were found. Carefully taken and studied routine microscopic sections, however, under the suspicion that the condition was really carcinoma, classified the case definitely as such. Section of a bronchus showed an infiltrating nodule, with prickle cells, whereas the pleural tumors continued to masquerade as endothelioma. Subsequent examination of the lungs, in the light of the microscopic findings, with a careful dissection of the bronchi, showed a small but definite nodular infiltration of the wall of the left main bronchus at the point of its dividing into upper and lower branches, with ulceration of the mucosa, and this proved to be typical epidermoid carcinoma. The circumstances of this case illustrate the pitfalls connected with this tumor, outwardly fitting as it does the conception of endothelioma of the pleura, and even

histologically not distinguishable from that neoplasm on the pleural state alone.

CASE REPORT

N. G., a 58 year old negro male, cook and laborer, was admitted to the Roper Hospital on the service of Dr. T. E. Bowers on June 16, 1934. His illness apparently began in January with a swelling in the neck, this increasing in size until the end of March, when it was as large as a small hen's egg and caused difficultv in talking and breathing but not in swallowing. At this time he thought he had a fever, which would last three to four days and then be absent for two to three weeks. The swelling gradually subsided to its present size. During April and May he began to lose weight. During the latter part of May a cough developed and the coughing spells would not be relieved until he had brought up a great deal of sputum. At no time had he coughed up blood. Also during the latter part of May, he began to have attacks of vomiting, these coming on several hours after solid food had been eaten. A pain developed in his right side, radiating towards his epigastrium, with indefinite relation to eating, possibly relieved somewhat by taking food. At no time had he vomited blood. Previous illnesses and family history appear irrelevant.

Examination revealed a thin and emaciated negro, temperature, 99°; pulse, 92; respirations, 28; blood pressure, 100/70. The cervical glands on the right, from the angle of the jaw to the clavicle were enlarged and hard, but were not tender nor adherent. The cervical glands on the left were only slightly enlarged. There were a few enlarged superficial veins over the chest. Expansion was fair and there were no abnormal areas of dullness detected. Bronchial breathing was heard in the right axilla from the third to the sixth ribs. Coarse râles were evident over the entire anterior chest, most marked in the lower portions. Examination of the heart area revealed no abnormalities; the radial arteries felt sclerotic. The liver margin was palpated one finger's breadth below the costal border; it was smooth and not tender. External hemorrhoids was the only other abnormal finding.

The urine was normal. The blood showed a hemoglobin of 70 per cent; leukocytes, 9,700, with 82 per cent polymorphonuclears, 16 per cent lymphocytes and 2 per cent eosinophiles. A Boas test meal gave a total acidity of 20 units and free HCl of 7 units. The chemical test for blood in the gastric contents was positive, but microscopic blood was not found. The sputum was bloody and watery, containing a large number of pus cells, but no tubercle bacilli could be found. Blood Kolmer and Kline tests were negative. A roentgen ray examination of the chest was reported as showing advanced bilateral fibrous pulmonary tuberculosis. A barium meal roentgenogram showed a pronounced ulcer deformity of the duodenal bulb with no obstruction.

During the patient's stay in the hospital he ran a low grade intermittent fever, the temperature rising to 99° to 100° almost every afternoon and falling

to normal during the night. There was no appreciable change in his condition until July 12, when he gradually became weaker, and he died the afternoon of that day.

A necropsy was performed on July 16, almost four days after death. The findings of note were: (1) the pleuro-pulmonary condition to be described later, (2) firm nodules over the peritoneal surface of the diaphragm, the mesentery, the capsule of the liver and the spleen, (3) marked enlargement of the mediastinal lymph glands and the right chain of cervical glands, with infiltration by a firm white tissue, (4) atherosclerosis of the aorta, (5) a simple ulcer of the duodenum and (6) a moderately granular kidney of about normal size.

The gross anatomical diagnoses were: primary endothelioma of the pleura, with metastases to peribronchial, tracheo-bronchial, peri-pancreatic and cervical lymph nodes and to the peritoneum; ulcer of the duodenum; atherosclerosis of the aorta; arteriosclerosis of the kidney.

The description of the lungs, amended following careful dissection after histological study is as follows.

The lungs were of approximately normal size. There was an emphysematous bleb about 2 cm. in diameter at the apex of the right upper lobe. The pleural surface was covered more or less uniformly by a dense pinkish white tissue. This was especially thick over the anterior portion of both lungs, where the lungs overlapped the heart borders, and here the covering was over 1 cm. in thickness. This thickening became less marked towards the lateral surfaces of both lungs, where it was seen as small flattened white nodules in the pleura. The flattened nodular structure was evident throughout, and even the thickest areas were seen to consist of coalescent nodules (figs. 1 and 2). The diaphragmatic surface on the right and to a lesser degree on the left, showed a thick layer of similar tissue. The mediastinal aspects of both lungs posteriorly showed an increased amount of this tissue similar to that seen anteriorly. The visceral pleura of the right lung on its posterior and lateral surfaces had been largely stripped away during the process of removing the lungs from the thorax. The pericardium was remarkably free of involvement, showing a few nodules on the inferior surface. The hilar lymph nodes were markedly enlarged in both lungs, and there was a node at the bifurcation of the trachea which was 3 cm. in diameter. All of these nodes showed the lymphoid tissue largely replaced by a dense pinkish white tissue. Anthracotic deposits were scattered throughout these nodes. The trachea and large bronchi were filled with a grayish mucoid secretion. The bronchi to the left lung were compressed by the enlarged lymph nodes. At the division of the left bronchus into its upper and lower branches, the bronchial wall was thickened and grayish white nodules were seen elevating the mucosa which showed granular surface ulceration. There was considerable narrowing of the bronchial lumen distal to this, and there was slight infiltration along the course of the bronchus. Distal to this, the corresponding lung tissue

FIG. 1. CARCINOMA OF PLEURA RESEMBLING ENDOTHELIOMA

FIG. 2. CARCINOMA OF PARIETAL PLEURA, RESEMBLING ENDOTHELIOMA

was somewhat atelectatic. Slender strands of dense tissue proceeded from this area to the near-by interlobar fissure which was markedly thickened by a tissue similar to that seen on the external surface of the lung The remaining bronchi to the left lung revealed no abnormality except a slight bronchiectasis. The bronchi to the right lung appeared normal throughout, although they were moderately compressed from without by the hilar lymph nodes. The interlobar fissures on the right were normal except for the anterior portion of the upper one as it approached the mediastinum, where it had a thickness of 3 mm. The lung itself was free of parenchymal nodules except at the lower portion of the left upper lobe where a number of small white nodules could be seen near the bronchial nodules described above. The lung tissue was unusually fibrous and resistant to cutting.

Microscopically, a section from the nodular infiltration described in the left lower main bronchus (fig. 3) showed erosion of the mucosa overlying a nodule which was just within the cartilaginous ring. This nodule was composed of fibrous bundles interspersed with strands of tumor tissue, arranged somewhat in loops, parallel to the mucosal surface of the nodule, passing between the mucous glands of the bronchus. These cells were fairly large, the nuclear chromatin was dense and darkly stained, and mitotic figures were not infrequent. Deep, to the cartilage, the tumor cells were arranged in larger clusters, somewhat differentiated into cuboidal cells at the periphery and tending to squamous cells towards the center, with an occasional eosinophilic "pearly body." Lymphatic invasion was quite marked and clusters of very active cells could be seen in these vessels. Some of the adjacent pulmonary alveoli were packed with tumor cells.

In the pleura (fig. 4) the differentiation was much less complete. The tumor cells were arranged in nests in the fibrous tissue, they were cuboidal, polyhedral, or compressed to simulate pavement cells, giving the histological picture accepted for pleural endothelioma. The nuclei were quite large and active. There was no squamous differentiation or pearly body formation, but careful examination revealed prickle cells, and these led the way to the discovery of the primary tumor and the conclusive diagnosis. Clusters of atypical cells were again seen in lymphatic channels. The pleural surface was generally thickened, partly by a hyaline fibrous tissue, but showing a considerable quantity of the tumor element. There were a few small collections of tumor cells in pulmonary alveoli subjacent to the pleura. Tumor growth was quite active and entirely similar in the interlobar pleura. The impression was gained that the tumor cells in the pleura were much more active and that the cancer was growing much more rapidly there than in the original focus in the bronchial wall.

In the hilar lymph glands, the tumor tissue seemed even more active than elsewhere. There was little differentiation, and the lymphoid tissue was almost completely replaced by the lobulated nests of atypical cells.

In addition to the neoplastic disease, there was widely scattered throughout both lungs an old fibrosis, generally in hyaline or nodular deposits containing black or opaque granular dust material. This was silicosis, and doubtless

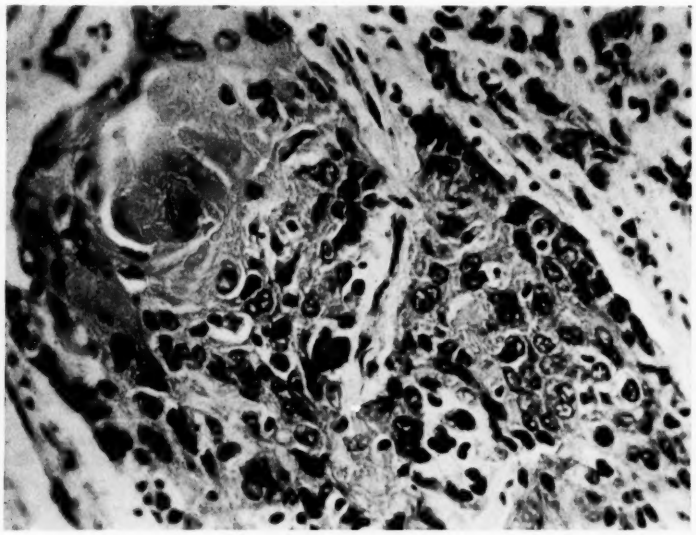
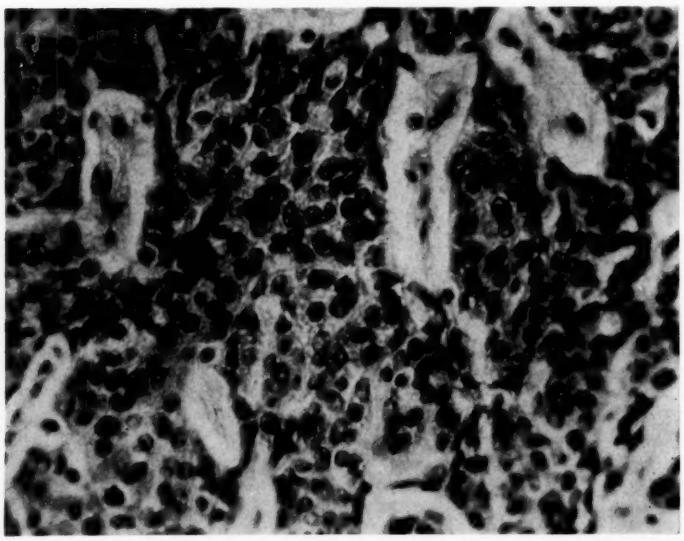


FIG. 3. PRIMARY EPIDERMOID CARCINOMA OF BRONCHUS
(Photomicrograph × 360)



UNIV. OF MICH.

FIG. 4. PLEURAL METASTASIS OF BRONCHIAL CARCINOMA
(Photomicrograph × 360)

accounted for the roentgen ray resemblance to fibrous tuberculosis. Its origin could not be traced, and its relation to the tumor is speculative but worthy of note, especially in view of the report of the high incidence of malignant disease of the lung in the Schneeburg miners.[3]

REFERENCES

(1) EWING, JAMES: Neoplastic diseases. Philadelphia: W. B. Saunders Company, p. 319, 1922.

(2) HARRIS, THOMAS: A contribution to the pathology and clinical features of primary malignant disease of the pleura. Jour. Path. and Bact., **2:** 174–189. 1894.

(3) PIRCHAN, A., AND SIKL, H.: Cancer of the lung in the miners of Jáchymov (Joachimstal). Am. Jour. of Cancer, **16:** 681–722. 1932.

(4) ROBERTSON, H. E.: "Endothelioma" of the pleura. Jour. of Cancer Research, **8:** 317–375. 1924.

(5) ZECKWER, I. T.: Mesothelioma of the pleura. Arch. Int. Med., **34:** 191–205. 1924.

ADRENAL DISEASE IN RELATIONSHIP TO HYPOGLYCEMIA AND DEATH*

JACK C. NORRIS

Grady Hospital, Atlanta, Georgia

Hypoglycemia is a common clinical entity and frequently becomes a serious problem to combat. Broadly considered the condition is present in two classes of patients. In one group the carbohydrate deficiency often results from malnutritive states, vomiting of pregnancy, acidosis or hyperinsulinism and for such cases glucose is a simple magic remedy.

In another group the patients are more seriously ill, often unconscious and in coma, having mild convulsions, and death seems inevitable. In these cases I suggest that diseased adrenals are an important factor in the etiology, thus suggesting an adrenal interrelationship with the liver, and finally that the condition is one of adreno-hepatic hypoglycemia.

CASE REPORTS

Case 1. A negro (W. H.), 36 years old, was admitted to Grady Hospital in March, 1934. He was in an unconscious state. The history revealed that upon returning home from his work he had fallen asleep and later could not be aroused. He had never been unconscious before and had previously seemed healthy. His wife stated that this "spell" followed a drink of whiskey given him by a friend. Others drank of the same whiskey without such effect.

The physical examination revealed a well formed man without evidence of trauma. He was having mild convulsive seizures and a Cheyne-Stokes type of respiration; his pulse was weak and rapid, and the blood pressure too low to be recorded accurately; his skin was cool and dry; pupils, round and equal; throat and mouth, normal. The lungs were negative; heart sounds, faint and distant; reflexes, equal and active. The spinal fluid was clear and under no increased pressure.

The urine examination showed slight albuminuria. The blood count was

* Read before the Thirteenth Annual Convention of the American Society of Clinical Pathologists, Cleveland, Ohio, June 8 to 11, 1934.

normal; blood sugar, less than 20 mgms. per 100 cc. Intravenous glucose and adrenalin stimulated him considerably and the blood pressure rose to 120 systolic and fell again to 100. Paraldehyde and glucose seemed to control the convulsions, but in spite of medication he died 24 hours after admission.

The necropsy revealed several old fibro-encapsulated abscesses in the lower lobe of the right lung. The esophagus and stomach were normal. The liver was of a chocolate-brown color, weighed 1500 grams, and revealed no gross evidence of disease. The histological study showed the liver cells to stand out quite well in an orderly manner. The sinusoidal spaces appeared normal. The nuclei of the cells stained fairly well. In some instances necrobiosis has ocurred. Kupffer's cells showed no evidence of disease effects. The bile ducts

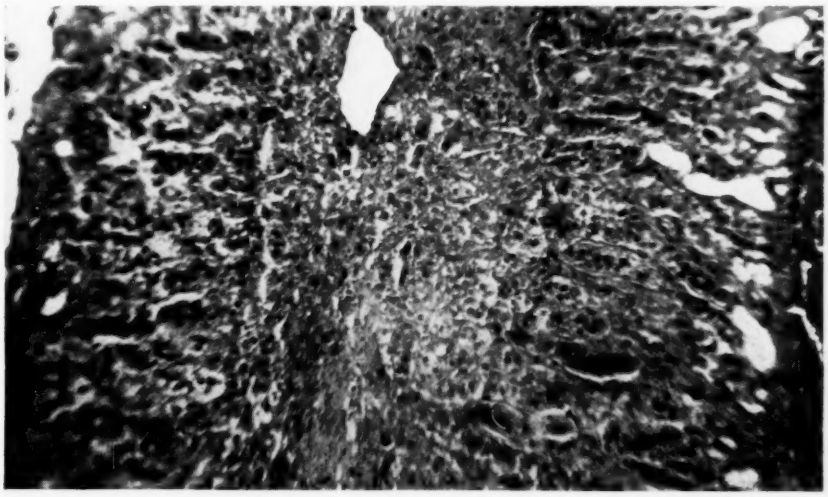


FIG. 1. SECTION OF ADRENAL

Shows the changes in the medulla and cortex described in the text. (Case 1)

were not occluded and the structural cells appeared normal. The blood vessels were not thrombosed. In some of the smaller vessels the blood content seemed hyalinized. The fibrous tissue was not increased. Areas of focal necrosis did not exist. Hemosiderin was not excessive in quantity.

The pancreas contained no adenoma. The interesting changes concerned the adrenals (fig. 1). They were located with difficulty and when found measured 2.5 cm. x 0.5 cm. in size. The color, shape and consistence were altered, and when sectioned seemed soft and contained a thin watery secretion, suggesting an atrophy and autolysis. The histological study showed fibrosis of the capsule, necrobiosis, atrophy and complete destruction of nearly all the cellular

structures. In the central portion there were many fibroblasts, infiltrating cells of all varieties, and areas of collected erythrocytes, indicative of a severe, progressive, generalized adrenalitis.

CLINICAL ANALYSIS

The symptoms and findings in the patient were of such serious proportions that little time for diagnosis was allowed. The convulsive seizures, the low blood pressure, and respiratory irregularity were treated symptomatically. The low blood carbohydrate was promptly treated by venifusions of glucose. As a diagnostic problem, some poison was considered such as methyl alcohol. Strychnine, arsenic, mercury, and cyanide were eliminated by the history, symptoms, and physical findings, and by chemical analysis of the stomach washings and later of the kidney and liver tissue. Uremia was possible, but uremia seldom manifests itself abruptly. The temperature and blood findings obviated infection. No reference or finding concerning cardiac disease was obtained. The final decision based on the low blood pressure, atypical mild convulsions, unconsciousness and the blood carbohydrate of 20 mgms. suggested hypoglycemia with circulatory failure. With the necropsy findings as previously presented the final diagnosis was bilateral chronic inflammatory, degenerative and atrophic adrenal disease with an associated mild hepatitis and hypoglycemia. The final and precipitating factor probably resulted from alcoholism.

Case 2. A negress (S. M.) was admitted to Grady Hospital on April 10 and died on April 12, 1934. She was in a semi-comatose state. She had been apparently well until March when she complained of pain which soon improved. On April 8 she became suddenly delirious and was put to bed. At this time her scleras were yellow in color. Her condition increased in intensity and she was quite unconscious when admitted to the hospital.

The physical examination was negative except for a pulse of 130, delirium, marked icterus, and hyperactive reflexes. Her blood pressure was normal. The laboratory examination revealed slight albuminuria; icterus index, 100; blood sugar, too low to determine; blood count, normal except for slight leukocytosis of 11,000; and an icteric spinal fluid.

The necropsy revealed an intense jaundice. The primary pathological change was in the liver. This organ was reduced in size, weighed 575 grams, was of a yellow-green color and had a roughened and semi-resistant surface.

Cut sections showed yellow scattered areas of liver cells with considerable interspersed fibrosis. Histologically, the liver showed diffuse blood pigment, general interlobular fibrosis with infiltrating cells, atrophy and degeneration of liver cells, with areas of actual hyperplasia of the bile ducts and liver elements. The adrenals showed considerable albuminous precipitation, a thickened capsule, and a slight general fibrosis. In many areas large numbers of the cells in the cortex and medulla were destroyed. In the pancreas many of the islets were larger than usual and were diagnosed as being hypertrophied.

CLINICAL ANALYSIS

The jaundice, unconsciousness, absent liver dulness, and low blood sugar suggested an acute and chronic hepatitis with hypoglycemia, and simulated those cases reported with cincophen poisoning. The necropsy confirmed the hepatitis and hypoglycemia and revealed a definite pathologic change in the adrenals and pancreas. There was no evidence or chemical findings of chemical poison. She was treated by stimulation and large quantities of glucose, given by vein, which seemed to aid temporarily. In spite of the quantity given, the anti- and postmortem blood sugars were less than 80 mgm. per 100 cc. In this patient there was definite evidence of liver insufficiency, yet histologically new liver cells were present. The hypoglycemia in such cases has been observed before, but little attention has been paid the adrenals.

Case 3. A patient (M. H.) was admitted to the hospital on January 31 and died February 1, 1934. She had suffered with indigestion for years. For three weeks she had been nauseated and occasionally emesis occurred. Lately her skin had turned in color from a light brown to black. Over the abdomen there was a peculiar bronzing effect. Her blood pressure was 100/60 on admission. The laboratory examinations revealed slight albuminuria, low blood sugar and leukocytosis. After being in the hospital for a few hours, during which time she received 50 per cent glucose and saline, she improved. Later she became suddenly comatose and her blood pressure dropped to zero. Adrenalin and glucose were given and after 50 cc. of 50 per cent glucose the blood sugar increased to 110 mgm. A few hours later she had a convulsive spell and died.

The necropsy revealed the liver to be smaller than usual, about 1200 grams in weight, and of a brown color. The adrenals were almost destroyed by a fibrocaseous tuberculosis. Histologically the liver contained small tubercles; otherwise it was normal. The kidneys showed a severe chronic nephritis. The pancreas had small scattered hemorrhages.

CLINICAL ANALYSIS

This last case is presented as a fairly typical Addison's adrenal tuberculosis with confirmatory necropsy findings. It is similar to the other two cases in the sudden collapse with low blood carbohydrate and death. The important fact was that the liver was not seriously affected and the hypoglycemia was obviously not entirely of hepatogenic origin.

PHYSIOLOGY OF THE ADRENALS, LIVER AND PANCREAS

It is sufficient here to summarize only the physiological responsibilities of these glands

The adrenal gland is largely responsible for the secretion of adrenalin and cortin. The importance of this organ seems paramount when we recall that through its harmones all structures related to the sympathetic nervous system are affected, including, of course, such important tissues as the heart, uterus, blood vessels and bronchi. Also it plays an important part in sex and physical development. It is of particular interest at this time to consider the relationship of the glands to the metabolism of sugar, and concerning this function it has been shown that the adrenal aids in the mobilization and conversion of glycogen into glucose.

Since the discovery of cortin by Swingle and Pfiffer further information concerning glycogenesis has been obtained. Britton[3] stated that the effect of adrenalectomy on carbohydrate metabolism is profound in character, and the effect on blood and liver carbohydrate metabolism is great. Hepatectomy gives an effect no more extreme than adrenal removal. Administration of cortico-adrenal extract brought about recovery of animals by restoring carbohydrate levels. He noted that during recovery of the animals following adrenal removal the amount of sugar fluctuated. Adrenalin alone is not effective. The cortical extract was active in dilutions 1:2,000,000. The conclusion is that carbohydrate metabolism may be considered as one principle function of the adrenal gland.

The liver has more than ten functions. One of the most im-

portant is that one concerned with sugar metabolism. It not only acts as a storehouse for glycogen, but acts in converting sugar from other sources such as protein. Mann and Magath[9,10] have contributed greatly to the knowledge of liver function through their experiments on dogs with extirpated livers. When the livers are removed there is a progressive and serious fall in the blood glucose and death soon ensues. It is also shown by these experiments that, while glucose tends to relieve the symptoms coincident with hepatectomy, the animals promptly die and the exact cause of death is unknown.

This organ is also concerned with sugar metabolism through the islets of Langerhan which secret insulin. Removal of the pancreas results in a fatal diabetes. It is believed that the pituitary secretions have a regulatory action on the islets depressing and preventing insulin from acting, this elevating the blood sugar. The islets are also acted upon to some extent by the vagus nerve and stimulation of the vagi will also cause transient fall in the blood sugar.

EXPERIMENTAL OBSERVATIONS

It is generally accepted as a fact that there is a coördinated function between the pancreas, liver and adrenals, especially in regard to the utilization of glucose. Considerable experimentation has evolved the liver-pancreatic association, yet little emphasis and attention has been accorded the adrenals. In fact several investigators think the adrenals of little importance in hypoglycemia. Stewart,[13] for instance, removed the adrenals from 200 dogs. He obtained hypoglycemia of moderate severity only, and that near death. Collens, Shelling and Byron[4,5] observed that exclusion of the hepatic arteries resulted in hypoglycemia and death. Epinephrine injected into these animals had no effect presumably due to the inability of the secretion to reach the organ. According to Mann,[8] Markowitz found that injections of adrenalin always evoked hyperglycemia. Mann and Magath[10] likewise have observed that epinephrine produced definite and prolonged hyperglycemia in anesthetized animals. Yet in animals whose livers had been removed the adrenalin evoked

no response or blood sugar increase, nor did it delay the symptoms of hypoglycemia. It seems, therefore, that definite proof exists of the relationship between the adrenal and liver as concerns glycogenesis.

CASE REPORTS CONCERNING ADRENAL HYPOGLYCEMIA

A considerable number of physicians have observed clinical syndromes particularly referable to the adrenals in patients in whom hypoglycemia occurred, Rabinovitch and Barden[12] had a patient with fatal hypoglycemia. The essential pathology was entirely in the adrenals. The medulla was affected by an inflammatory process mostly lymphocytic and fibroblastic. Likewise they reported a case in which the hypoglycemia was the result of a pancreatic tumor of an adenomatous nature. Anderson[1] reported an adrenal cortical carcinoma which produced fatal hypoglycemia. He concluded that "it must be admitted that disturbances in the functions of other glands may be important factors in causing a pathologically low blood sugar."

It is generally known that hypoglycemia is concerned with the hepatitis of subacute atrophy and cincophen poison. Cross and Blackford[6] reported a patient with fatal hypoglycemia, presumably caused by arsenic. The liver was damaged severely. The adrenals were not examined histologically. In similar cases, however, degenerative adrenal lesions have been observed. Blumgarten[2] in a clinical discussion of hypoglycemias stated that the adrenal is important in carbohydrate metabolism and he presented a case with adrenal insufficiency. Of especial interest is a presentation of Mosenthal, Ashe, Poindexter and MacBrayer,[11] of a patient with hypertension and an associated hypoglycemia. It was important that they noted that the blood sugar decreased as the blood pressure rose. Particularly was this a notable finding during the stages of hypoglycemia. At necropsy the essential pathology was in the kidneys. The pancreas, however, showed an islet hypertrophy. There was also a periadrenal hemorrhage with inflammatory changes.

In a series of patients, one of which is considered in this paper, it seems that in brief the clinical features are as follows. For a

period of time there may be periodic attacks of general weakness and partial collapse; the patient may complain of dizzy spells and of nausea and headache. In the more pronounced cases the onset may be sudden and general weakness is followed by nausea, twitching of muscles, nervousness, rapid or slowed heart rate, exaggerated reflexes, and a subnormal temperature with a tendency to perspire freely. A later stage surely follows and a precipitate semiconscious state ensues which in several instances has followed alcoholism. The pulse varies and may be fleety and rapid, the respiration irregular. Repeated mild convulsions occur and coma deepens. The blood pressure is low or normal, though at times it may fluctuate (this was observed particularly in a patient whose blood sugar was 60 to 70 mgm. and who had bilateral adrenal carcinoma). The blood sugar is low, usually 20 to 60 mgm. In a few hours, regardless of treatment, death occurs. I have performed necropsies on an infant and on adult, who suddenly presented severe symptoms of collapse. The blood sugars at post mortem were too low to determine. Death had been immediate and inexplainable. Both previously had had a mild influenzal-like infection seemingly of little consequence. I found in each instance large hemorrhages in the adrenals.

It is interesting to compare those symptoms with those of late Addison's disease as they are in many instances identical. Further comparison is important as relates to the adrenalectomized animal. Here the animal has a rapidly beating heart, weakness, respiratory irregularity and coma. Low blood carbohydrate and low pressure is noted. In the hepatectomized animal, as observed by Mann and Magath the onset of symptoms is sudden; at first muscular weakness occurs with loss of reflexes. Later the reflex activity returns and are exaggerated. Muscular twitchings then appear and later general convulsions, coma and death. The blood pressure may fluctuate, being subnormal before death. The pulse is rapid. In coma the respiration may be of the Cheyne-Stokes type. The heart often continued to beat for quite a while after respiratory failure. This observation concerning respiratory cessation is most important and is noted later in regard to treatment.

The adreno-hepatic hypoglycemia syndrome may be confused with several pathologic states. Cyanide poisoning produces a chain of symptoms that very closely simulate severe adrenal deficiency. Yet the cyanides kill rapidly; the blood is pinkish red and the odor of cyanide may be present in the tissues. There is usually a history of suicidal intent. I have found only one reference to the adrenal in cyanide poisoning and I feel certain that the adrenals and liver are affected. In this instance, according to Webster,[14] Forst has shown that glucose and insulin will protect an experimental animal against large quanities of hydrocyanic acid. With the information at hand it is logical to hypothecate adrenal-liver damage in cyanide poison.

Other diseases which must be differentiated are uremia, severe internal hemorrhage, diabetic coma, acidosis, cerebral hemorrhage, cardiac failure, ruptured heart or aorta, and acute alcoholism.

On the basis of clinical observations in the human and experimental findings in the animal, the following classification for hypoglycemia is proposed:

(1) Hypoglycemia due to hyperinsulinism.

(2) Hypoglycemia of hepatogenous origin, associated with starvation states, pernicious vomiting, brain tumors, pellagra, obstructions, hepatic tumors, et cetera.

(3) Hypoglycemia due to adrenal disease, tuberculosis, atrophy, subacute adrenalitis, tumors, et cetera.

(4) Hypoglycemia resulting from poisons, cyanides, salvarsan, cincophen.

(5) Hypoglycemia of mixed etiology caused by hepatic and adrenal disease in combination.

(6) Hypoglycemia associated with nephritis and hypertension and arteriosclerosis.

(7) Hypoglycemia, traumatic, infectious, with hemorrhage into adrenals.

TREATMENT

Regardless of past therapeutics the adreno-hepatogenous hypoglycemias have been fatal, yet the hope of future success by treatment is encouraging. Facts largely obtained through animal experimentation especially as regards glucose and cortin is of aid. Harrop[7] and his associates have observed that in supra-

renalectomized dogs in spite of severe symptoms, cortical-renal extract, glucose and chlorides restored them to normal.

While experimental medicine often discloses valuable facts, those facts and principles do not always work satisfactorily when applied to the human. However, it seems logical that any treatment of the adreno-hepatic hypoglycemia should be in accord with experimental knowledge. Therefore, it is suggested that the administration of glucose in large quantities with cortin and chlorides be tried. The respiratory failure should be combated with respiratory stimulants. The heart should be digitalized. Heat externally should be applied. For the convulsive states amytal and morphine in limited amounts would seem sufficient. Paraldehyde is contraindicated because I have recently seen an incidence of poisoning by the drug and the patient's blood sugar was very low and continued low even after glucose administration.

REFERENCES

(1) Anderson, H. B.: A tumor of the adrenal gland with fatal hypoglycemia. Am. J. Med. Sci., **180:** 71–79. 1930.

(2) Blumgarten, A. S.: Spontaneous hypoglycemias in endocrinopathies. Med. Clin. N. Amer., **17:** 80–89. 1933.

(3) Britton, S. W.: On the apparent principal function of the adrenal glands. Am. J. Physiol., **101:** 14. 1932.

(4) Collens, W. S., Shelling, D. H., and Byron, C. S.: Studies on the physiology of the liver. I. Effect of ligation of the hepatic artery on carbohydrate metabolism. Am. Jour. Physiol., **78:** 349–357. 1926.

(5) Collens, W. S., Shelling, D. H., and Byron, C. S.: Studies on the physiology of the liver. II. Effect of adrenalin upon blood sugar following ligation of the hepatic artery. Am. Jour. Physiol., **79:** 689–693. 1927.

(6) Cross, J. B., and Blackford, L. M.: Fatal hepatogenic hypoglycemia following neo-arsphenamine. Jour. Am. Med. Assn., **94:** 1739–1742. 1930.

(7) Harrop, G. A., Weinstein, A., Soffer, L. J., and Trescher, J. H.: Studies on the suprarenal cortex. Jour. Exp. Med., **58:** 1–16. 1933.

(8) Mann, F. C.: Effects of complete and partial removal of liver. Medicine, **6:** 419–511. 1927.

(9) MANN, F. C., AND MAGATH, T. B.: Studies on the physiology of the liver. II. The effect of the removal of the liver on the blood sugar level. Arch. Int. Med., **30:** 73–84. 1922.

(10) MANN, F. C., AND MAGATH, T. B.: Studies on the physiology of the liver. III. The effect of the administration of glucose in the condition following total extirpation of the liver. Arch. Int. Med., **30:** 171–181. 1922.

(11) MOSENTHAL, H. O., ASHE, B. I., POINDEXTER, C. A., AND MACBRAYER, R.: Spontaneous hypoglycemia occurring in the course of essential hypertension. Med. Clin. N. Amer., **17:** 41–65. 1933.

(12) RABINOVITCH, JACOB, AND BARDEN, F. W.: Hypoglycemia associated with a tumor of the islands of Langerhans and with adrenal insufficiency, respectively. Am. Jour. Med. Sci., **184:** 494–503. 1932.

(13) STEWART, G. N.: The adrenal glands. Arch. Int. Med., **43:** 733–766. 1929.

(14) WEBSTER, R. W.: Legal medicine and toxicology. Philadelphia: W. B. Saunders and Company, pp. 696–830, 1930.

A POSTMORTEM ANALYSIS AS TO ETIOLOGY IN ONE THOUSAND CASES OF PERITONITIS*

C. C. PFLAUM

From Department of Pathology, University of Missouri School of Medicine, Columbia, Missouri

The literature on the subject of peritonitis is voluminous. The Quarterly Cumulative Index for 1931 lists a total of 141 papers on this subject. These papers are largely concerned with the report of cases of unusual interest, or with the study of a series of cases of one definite type. The author was unable to find an analysis of the etiologic factors concerned in the production of a large series of cases of general peritonitis. The textbooks, while discussing the general etiology of the disease, do not give any approximate percentage of the relative frequency with which the causative factors operate. It seemed worth while, therefore, to study a series of postmortem examinations of sufficiently large number with the intent to determine the frequency of general peritonitis, its etiology and variations incident to age and sex.

This report is based on the study of the records of 14,263 necropsies performed by members of the Department of Pathology of the University of Minnesota extending from 1920 to 1932. This autopsy material came from the various hospitals, the coroner's service, and non-hospitalized patients of the City of Minneapolis and from Ancker, Miller and St. Luke's Hospitals of St. Paul. The cases represent a variety of general and specialty hospital material, and were the patients of several hundred practicing physicians. The necropsies were performed and recorded by some twenty pathologists. This multiplicity of practitioners and pathologists should make possible a more comprehensive and unbiased survey than would be the case were the material all from one hospital and one staff group.

* Read before the Thirteenth Annual Convention of the American Society of Clinical Pathologists, Cleveland, Ohio, June 8 to 11, 1934.

A total of 14,263 consecutive necropsy records were examined, and those concerned with general peritonitis were studied in detail as to sex, age, cause of the condition, whether or not operation had been done, et cetera. This study yielded an even 1000 cases of peritonitis. This is equivalent to 7 per cent of all the necropsies. There were, however, 1,335 examinations on the bodies of stillborn infants, which when deducted from the total number of necropsies, makes the incidence of peritonitis rise to

TABLE 1

YEARLY INCIDENCE OF PERITONITIS*

YEAR	NECROPSIES	PERITONITIS	
		cases	*per cent*
1920	450	34	7.55
1921	554	56	10.10
1922	639	58	9.07
1923	724	67	9.25
1924	737	82	11.13
1925	946	55	5.81
1926	1089	83	7.62
1927	1203	99	8.23
1928	1571	108	6.87
1929	1731	99	5.72
1930	1782	167	9.37
1931†	1502	92	6.12
Total.....	12928	1000	

* Exclusive of necropsies on stillborn infants, which amounted to 1335 during the period under study.

† Not entire year.

7.73 per cent. Table 1 shows the variation from year to year in this percentage. Brines,[1] in a recent analysis of 1,535 necropsies, found 94 cases (6 per cent) to have general peritonitis.

SEX AND AGE

There were 525 cases, or 52.5 per cent in males, and 475, or 47.5 per cent in females. In the general necropsy series, however, the ratio of males to females is practically 2 to 1. Taking this into consideration, peritonitis is seen to be considerably more

frequent in the female. As will be noted in the succeeding paragraphs, the female is subject to most of the etiologic factors operative in men plus those peculiar to her sex.

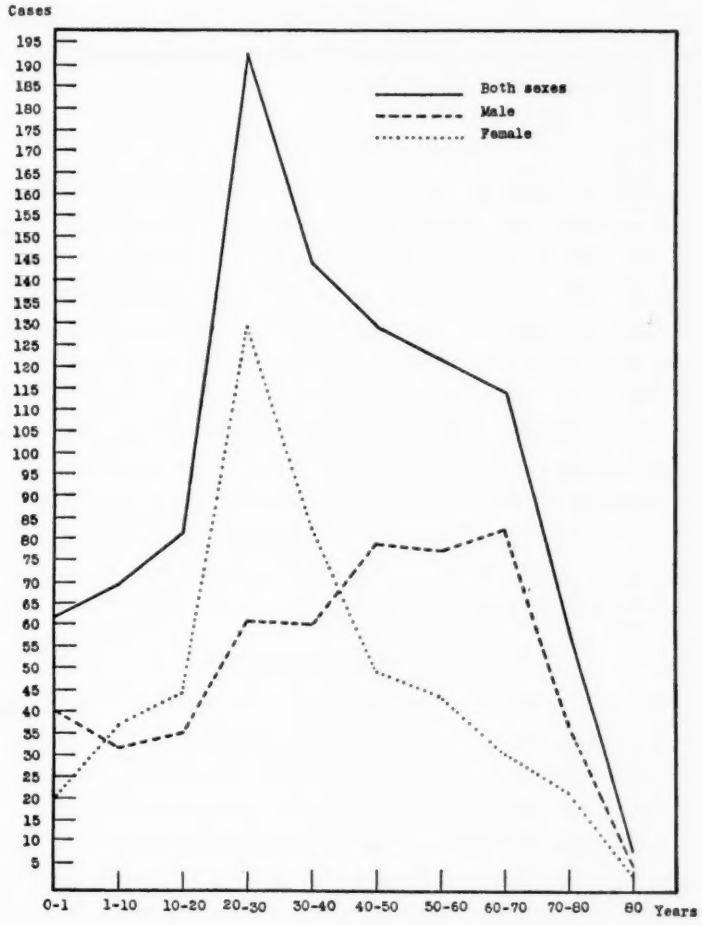


CHART 1. AGE AND SEX DISTRIBUTION OF 1000 CASES OF PERITONITIS

The age incidence is graphically shown in chart 1. The greatest number of cases per decade occur in the group of 20 to 30 years. This is the period in which appendicitis, tuberculosis and abortion play important rôles. The curve for females corre-

sponds quite closely with the general curve, because the cases related to gynecologic and obstetric pathology also have their peak in the same decade. The male group reaches its peak at a later age; namely 40–70 years. The cases of peritonitis causing this peak are those following perforated gastric and duodenal ulcers, and carcinomata, all of which occurred predominately in the male sex, and at an average age of 50 years

BACTERIOLOGY

Studies were made on the peritoneal exudate of 112 cases (11.2 per cent). This may seem to be a low percentage of such examinations, but in many cases the bodies had already been embalmed; in others the interval between death and necropsy was so long that postmortem secondary bacterial invasion was very probable, and still other bodies were examined under circumstances that made such examination impossible.

The most common organism was found to be a streptococcus eighty-four cases, or 75 per cent); next in frequency was a staphylococcus in nine cases; colon bacilli, seven cases; pneumococcus, six cases; typhoid bacillus, two; a Gram positive diplococcus, two; a spore bearing aerobe, one; and gonococcus, one. Five of the six cases due to pneumococci occurred in females.

CLASSIFICATION OF CASES

In most cases the proper etiologic classification was immediately apparent, as in cases of perforated ulcer. In other cases, even after careful study of the available clinical and postmortem data, the proper place for the case in question was difficult to decide. The classification as finally adopted is shown in table 2. The cases are arranged in their order of frequency of occurrence. It is possible to group together some of the factors listed separately; otitis media, erysipelas, septic throats, et cetera, might be classed together as a distant focus of the peritoneal inflammation, but for emphasis are listed separately.

POST-OPERATIVE PERITONITIS

The largest single group of cases, 221, followed abdominal or pelvic surgical procedures (table 3). Cases of a perforated viscus,

such as ruptured peptic ulcer, traumatic perforation of intestine, and those with a gangrenous organ, as an appendix, were not included in this group, even though many such cases were operated

TABLE 2

ETIOLOGIC CLASSIFICATION OF 1000 FATAL CASES OF PERITONITIS

CAUSATIVE FACTOR	MALES	FEMALES	TOTAL	PER CENT OF ALL CASES
Post operative	125	96	221	22.1
Acute appendicitis	86	40	126	12.6
Tuberculous peritonitis	56	44	100	10.0
Post-abortion		77	77	7.7
Malignant tumors	39	25	64	6.4
Perforating peptic ulcer	37	11	48	4.8
Undetermined (primary)	22	23	45	4.5
Post-traumatic	35	6	41	4.1
Pelvic inflammations		37	37	3.7
Miscellaneous intestinal lesions	15	16	31	3.1
Puerperal infections		25	25	2.5
Ulcerative colitis	7	8	15	1.5
Otitis media	9	6	15	1.5
Intrathoracic disease	11	4	15	1.5
Hepatic and gall bladder lesions	7	7	14	1.4
Pyemia or septicemia	7	6	13	1.3
Strangulated hernia	6	7	13	1.3
Mesenteric thrombosis	9	3	12	1.2
Renal lesions	6	5	11	1.1
Perforated typhoid lesions	8	2	10	1.0
Umbilical infection	7	3	10	1.0
Perforated tuberculous lesions	6	3	9	0.9
Perforated intestinal diverticulum	5	4	9	0.9
Acute cystitis	8	1	9	0.9
Adjacent suppuration	6	2	8	0.8
Erysipelas	1	6	7	0.7
Septic sore throat	2	4	6	0.6
Acute pancreatitis	2	3	5	0.5
Phlegmonous gastritis	2		2	0.2
Bacterial endocarditis	1	1	2	0.2
Total	525	475	1000	100.0

upon and subsequently died of general peritonitis. The sex incidence of the 221 cases was 56.5 per cent males, and 43.5 per cent females.

TABLE 3

LESIONS AND TYPES OF OPERATIONS IN 221 POST-OPERATIVE CASES OF PERITONITIS

GROUPED LESIONS	PROCEDURE	MALE	FEMALE	TOTAL
Gastric (42)	Resection for carcinoma	22	3	25
	Gastro-enterostomy for peptic ulcer	7	4	11
	Pyloroplasty, scars from peptic ulcers	1	1	2
	Remsted operation. Pyloric stenosis	2	0	2
	Gastrostomy, carcinoma of larynx	0	1	1
	Resection of gastric ulcer	1	0	1
Colon and rectum (41)	Resection of colon for carcinoma	13	6	19
	Resection of rectum for carcinoma	5	4	9
	Colostomy	7	2	9
	Cecostomy	3	0	3
	Hemorrhoidectomy	1	0	1
Gynecologic (30)	Hysterectomy		11	11
	Salpingectomy		5	5
	Uterine suspension		3	3
	Caesarian section		3	3
	Tubal pregnancy		2	2
	Removal of ovarian cyst		2	2
	Pelvic floor repair		1	1
	Uterine curettage with perforation		1	1
	Instrumentally induced labor		1	1
	Bilateral oophorectomy		1	1
Gall bladder (28)	Cholecystectomy	9	11	20
	Cholecystostomy	3	3	6
	Cholecyst-gastrostomy (Ca. of pancreas)	2	0	2
Appendiceal	Appendectomy	13	7	20
Small intestine (17)	Procedures for relief of intestinal obstruction	3	6	9
	Resection of segment of intestine	3	2	5
	Resection of intestinal fistulae	1	2	3
Genito-urinary (12)	Prostatectomy	6		6
	Nephrectomy	1	1	2
	Removal of ureteral stone	1	1	2
	Resection of carcinoma of bladder	0	1	1
	Hemorrhagic ureteritis	1	0	1
Not known	Exploratory laporatomy	5	6	11
Ascites	Paracentesis	8	2	10
Hernia	Herniotomy	2	3	5
Pancreatic	Palliation of carcinoma of pancreas	3	0	3
Splenic	Splenectomy	2	0	2
Total		125	96	221

Surgical measures for the relief of gastric disease head this group, with forty-two cases, or 19 per cent. The type of lesion or operative procedure is shown in table 4. The high incidence of peritonitis following gastric surgery is undoubtedly due to the great technical difficulties involved, especially the difficulty of securing water-tight suture lines. Indeed, in many of the cases a point of leakage was readily demonstrable at necropsy.

Peritonitis developing after operations on the large bowel is the next most frequent type of post-operative occurrence of this disease. There were forty-one such cases, twenty-nine of which were in males. The majority of operations were for the eradication or palliation of carcinoma.

Gynecologic cases follow with a total of thirty post-operative deaths. There were nineteen operations upon the uterus, seven upon the uterine tubes, three upon the ovaries, and one a perineal repair. Of the entire group, six were immediately associated with pregnancy.

Gall bladder surgery was followed by general peritonitis in twenty-eight cases equally divided as to sex. There were twenty cholecystectomies for cholecystitis and cholelithiasis, six cholecystostomies for the relief of obstructive jaundice caused by malignant tumors, and two cholecystogastrostomies. In some of these cases, the appendix was also removed.

There were twenty appendectomies in which the history revealed that operation was performed for chronic disease of the appendix. All acute appendices removed and followed by peritonitis are listed under the group of appendicitis and not in the post-operative group.

Operations on the small intestine constitute seventeen cases of this group. The majority of the procedures were for the relief of intestinal obstruction.

A wide variety of genito-urinary operations were followed by peritonitis in twelve cases, half of which were for the removal of the prostate.

Exploratory laporatomy resulted in death from peritonitis in eleven instances. This procedure revealed an inoperable carcinoma of the stomach in five cases, cirrhosis of the liver in four, and carcinoma of the large bowel in the remaining two.

Paracentesis, a procedure which is too frequently regarded as a minor one, was responsible for ten cases of post-operative peritonitis. The measure was carried out on patients suffering from: gastric carcinoma, congenital heart disease, hepatic cirrhosis, mesenteric cyst, nephrosis, and tuberculous peritonitis. In the last instance, it was demonstrated that the trocar had perforated an intestinal loop.

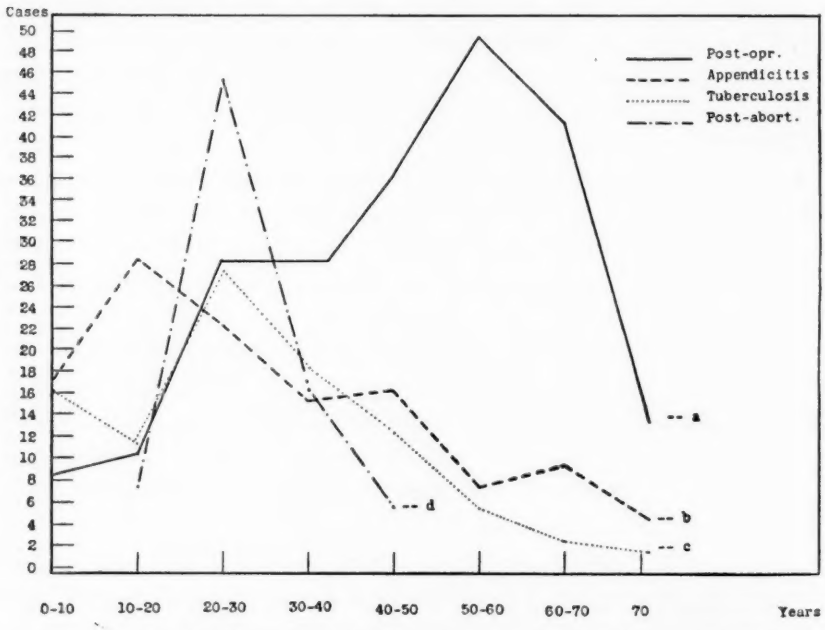


CHART 2. Age incidence in (a) 221 cases of post-operative peritonitis; (b) 126 cases of peritonitis associated with appendicitis; (c) 100 cases of tuberculous peritonitis; and (d) 77 cases of post-abortive peritonitis.

Herniotomy in five cases, operations upon three patients for the palliation of pancreatic carcinoma, and two splenectomies complete this group. The spleen was removed in one instance because of Banti's disease, and in the other because of thrombocytopenic purpura.

Chart 2 (a) giving the age groups of the post-operative cases shows two peaks in the curve. The first peak is due mainly to

the appendiceal and gynecologic cases, while the second and highest point on the graph is due largely to the operations for the eradication or palliation of carcinoma.

ACUTE APPENDICITIS

Acute inflammation or gangrene of the appendix, with or without perforation, resulted in a fatal general peritonitis in 126 cases. Males predominated, with 68 per cent. Most of the patients were operated upon and general peritonitis was discovered, but operations were not performed on twenty-six patients, or 20 per cent. The age incidence is shown in chart 2 (b), the age extremes being 2 and 88 years.

TUBERCULOSIS OF PERITONEUM

It is interesting, if not surprising, to note that tuberculosis should be third in frequency of factors causing peritonitis. This may be partly due to the fact that the material on which this analysis is based includes the patients of several large services caring for tuberculous patients, and partly because necropsies are more likely to be asked for in cases of this nature. There were 100 cases (10 per cent of the cases under study, or 0.7 per cent of this entire necropsy series) of peritoneal tuberculosis, and nine additional cases in which a general purulent peritonitis followed the perforations of tuberculous intestinal ulcers.

The sex incidence of the one hundred cases was 56 per cent males and 44 per cent females. In fifty-six, there was an active pulmonary tuberculous lesion. In twenty-six cases the peritoneal lesion was part of a general miliary tuberculosis (in ten of these a tuberculous meningitis was discovered at necropsy). A definite intra-abdominal source of the peritoneal lesion was discovered in eight-four instances; namely, tuberculous enteritis, colitis, or both, forty-three cases; salpingitis in sixteen; caseous mesenteric lymphadenitis in thirteen; renal tuberculosis in five; tuberculosis of prostate and seminal vesicles in four; and adrenal lesions in three. The age incidence of this group is graphically shown in chart 2 (c).

GYNECOLOGIC AND OBSTETRIC CASES

The dangers of induced abortion cannot be overemphasized. There were seventy-seven cases of fatal peritonitis following induced abortions. This is more than 16 per cent of the female cases under study. Most of these cases were referred by the coroner, and while many of the histories obtained were very meager, it seems likely that most of the abortions were either self-induced or done by some nonmedical individual.

The age incidence of the patients is shown in chart 2 (d). The following genital lesions were observed at necropsy: acute or gangrenous endometritis in fifty-two cases, acute salpingitis in eight, six cases of tubo-ovarian abscess and three with definite gross perforation of the uterus, one of which also had a perforated loop of ileum. Bacteriologic examinations were made on the peritoneal fluid of nine cases. The organism was a streptococcus in eight cases (a hemolytic streptococcus in four) and a staphylococcus in the remaining case.

In spite of better obstetric care, peritonitis is still a complication to be borne in mind in the puerperal patient. In this series of 1000 cases, twenty-one women with an average age of twenty-seven years, died of peritonitis following full term parturition. The fatal outcome resulted in a week to ten days after delivery in most cases, but was delayed in one instance for a month and in another for six weeks. Instrumentation, as forceps, use of the Vorhees bag, et cetera, was employed in five cases; one case had a breech presentation, and another had a placenta praevia. Labor was induced in one patient by the use of quinine. The associated pathologic findings were stated in sixteen cases as follows: acute or gangrenous endometritis in twelve cases and acute suppurative salpingitis in four.

There were three cases of uterine rupture during labor at full term. Two cases occurred during intra-uterine manipulations. In one case a craniotomy was done in a 21 year old woman suffering from Pott's disease, and in the other a transverse presentation was being corrected. The third case occurred in a 45 year old primipara. There was one case associated with abdominal

pregnancy which had progressed to about full term, when maceration of the fetus and general peritonitis occurred.

An important source of peritonitis is acute or chronic inflammation of the female pelvic organs. In the series, 3.7 per cent of all cases (7.8 per cent of the total female cases) died of peritonitis, the origin of which was in the tubes or ovaries. Pregnancy was not a factor in this group. The original inflammation was located in the tubes and ovaries in fourteen cases; in the tubes in thirteen cases, eleven of which were acutely affected; in the ovaries in two cases, and in the remaining eight cases, the inflammation had produced a general plastic pelvic cellulitis. Operations were done on ten of these women. The age of the patients varied from 5 to 74 years, nineteen being between 20 and 40, while the average age was 32. Only eight were investigated bacteriologically. Streptococci were found in six cases, and pneumococci and gonococci each in one case.

MALIGNANT TUMORS

The most frequent cause of peritonitis in patients over 50 years of age was perforation of a viscus by malignant neoplasms. There were forty-two such cases in this series, thirty being in men. The conditions encountered were thirty-eight carcinomas, two sarcomas, one hypernephroma, and one case of Hodgkin's disease.

The locations of the tumors were:

Carcinoma of stomach, 12 cases
- 11 males, whose average age was 61 years.
- 1 female, aged 70.

Carcinoma of sigmoid, 7 cases
- 4 males, with an average age of 64 years.
- 3 females, with an average age of 55 years.

Carcinoma of transverse colon, 6 cases
- 4 males, with an average age of 53 years.
- 2 females, with an average age of 53 years.

Carcinoma of rectum, 5 cases
- 3 males, average age, 59 years.
- 2 females, average age, 44 years.

Carcinoma of cecum, 2 cases
Both males, average age, 33.5 years.

Carcinoma of pancreas, 2 cases
Both males, average age, 63 years.

Carcinoma of duodenum, 2 cases
One male aged 55, and 1 female, 47.

Sarcoma of stomach, 2 cases
One male aged 35, 1 female, 69.

Carcinoma of bladder, 1 case (male, 66).
Carcinoma of gall bladder, 1 case (female, 60).
Hodgkin's disease, perforation into ileum (female, 26).
Hypernephroma perforating colon (male, 73).

Operative repair of the perforation was attempted in only six of the forty-two cases.

There were twenty-two additional cases of carcinoma which had extended to and involved the peritoneum but in which no gross perforation of a viscus could be demonstrated. The average age of the nine males was 58 years, and that of the thirteen females was 51 years.

The types of lesions follow:

8 cases of carcinoma of stomach (one with necrosing omental metastasis)
8 cases of uterine carcinoma
2 carcinoma of body
6 carcinoma of cervix (4 had received radium therapy)
2 cases of carcinoma of urinary bladder
1 case of carcinoma of prostate
1 case of carcinoma of sigmoid
1 case of generalized carcinomatosis of gland cell type, primary not determined
1 case of multiple malignant melanomata of the small intestine.

PEPTIC ULCER

Nearly 5 per cent of the fatal cases of peritonitis resulted from the perforation of a peptic ulcer. The ulcer was located in the duodenum in thirty-two instances, twenty-seven being in males. The ulcer was single in all except one case, in which there were multiple ulcers, but only one had perforated. The age of the patients ranged from 12 to 81 years, with an average of 49. The youngest patient also had a sarcoma of the cecum.

The sex incidence of the sixteen cases of perforated gastric ulcer was ten males and six females. The ages varied from 18 to 76 years, with an average age of 54. The ulcers were all located near the pylorus except one, which was near the cardia. One male of 18 years received a second degree burn of the abdomen shortly before the peritonitis began.

Operative repair was attempted on twenty-one patients of this group, but in most of them peritonitis was already present. In one instance of duodenal ulcer, the perforation was not located at operation.

PRIMARY PERITONITIS

Neither an intra-abdominal source nor a distant focus of infection could be demonstrated in forty-five cases of general peritonitis of which twenty-two were males and twenty-three females. Because of the absence of any assignable cause, this group is considered as primary peritonitis. One-third of the patients were under 1 year of age, the remainder being rather evenly distributed in age from 1 to 70. Laparotomy was done on eight patients, but in each instance a general peritonitis of undetermined origin was already present. Bacteriologic studies made on twenty of these cases revealed a streptococcus in sixteen, staphylococcus in two, pneumococcus and a diplococcus in one case each.

POST-TRAUMATIC PERITONITIS

An important factor in general peritonitis is trauma. Males, as might be expected, predominated in this group of forty-one cases, the ages ranging from 4 days to 83 years, but a third of them occurred in the 30–40 year decade. Automobile accidents, falls, blows received in fights, (that is, blunt trauma) resulted in twenty-two cases of peritonitis. In fourteen of these there was perforation or rupture of the small intestine, perforations of the urinary bladder in three, rupture of spleen and of liver in two cases each, and fracture of the pelvic bones in one instance. In the latter an exploratory laparotomy was done, but no visceral lesion was found. Two cases also had skull fractures.

Gunshot wounds were followed by a fatal peritonitis in sixteen

cases. Visceral injuries resulting were perforations of small intestine in eight, colon, five, stomach, three, liver, two, and bladder, one. One case developed a purulent empyema, but had no intra-abdominal perforations, but had an exploratory laparotomy. Stab wounds account for two cases. One of the earliest deaths from peritonitis occurred in a 4 day old infant in whom birth injuries resulted in a ruptured colon.

LESIONS OF THE DIGESTIVE ORGANS

General peritonitis terminated the course of ten cases of typhoid fever. Males predominated in the ratio of eight to two. Definite perforation of the intestinal ulcerations was demonstrated in eight instances, these being located in the terminal ileum in six cases, once each in the cecum and at the ileo-cecal valve. The average age of this group was 33 years, the extremes being 7 and 53 years. It is interesting to note that 60 per cent of the cases occurred in the first third of the time period under study. This is in keeping with the decreased incidence of typhoid fever in the urban districts incident to better sanitation and to prophylactic therapy.

Ulcerative colitis was an etiologic factor in fifteen patients, seven males and eight females. In only seven of these cases was a gross perforation of the colon demonstrated. One perforation had been surgically repaired. The average age of this group was 36.5 years.

Incarcerated hernia with resultant gangrene of intestine accounted for thirteen cases of peritonitis. The six males and seven females had an average age of 59 years. Operative relief was attempted in six cases, but in each there was a purulent peritoneal exudate present at the time of operation. The type of hernia was femoral in five cases; inguinal in four, intra-abdominal in three, and ventral in one.

Thrombosis of the superior or inferior mesenteric vessels was the etiologic factor in twelve cases, nine of which were males. Gangrene of the ileum, or of both ileum and ascending colon, was present in all of these cases. Operation was done on five patients, but a non-viable gut and beginning peritonitis rendered

the procedure hopeless. The advanced average age of this group (68 years) suggests that arteriosclerosis is the basic factor of the thrombosis.

Acute inflammation of intestinal diverticula with resultant gangrene or perforation caused death by peritonitis of nine patients. A Meckel's deverticulum was the site of the lesion in three instances. Inflammation of sigmoid diverticula was present in the remaining six. Operation was carried out in three cases, all with a pre-operative diagnosis of appendicitis. The average age of this group was 45 years, with extremes of 8 and 71 years.

There were eight cases of intestinal obstruction, five in women. Two were due to adhesions from a previous operation, one occurring in a 4 day old infant being due to a mesenteric anomaly. In two cases, perforation of the distended gut occurred.

In a group of six cases, necropsy disclosed intestinal perforations, the etiology of which was not determined. The lesions were quite definitely not typhoid or tuberculosis. The perforations were located in the cecum in four instances, and in the lower ileum in the remaining two. Bacteriologic examination of two cases (both cecal perforations) revealed a streptococcus.

Intussusception occurred in five cases, four of which were males, four being less than 1 year of age. Perforation of the intestine occurred in one case. There were four cases of fecal fistulae, all in women, and in two cases were associated with carcinoma of the uterus. Volvulus occurred in three cases, one being a male 76 years of age. There were three cases of congenital atresia. In two cases the lumen of the colon was absent, and in one, the upper ileum was affected. Perforation of the gut occurred in two instances.

Phlegmonous inflammation of the wall of the gastro-intestinal tract may extend to and involve the peritoneum. There were two cases of phlegmonous gastritis both in males aged 50. In one there was an ulcerating gastric carcinoma. The third case was that of a girl of 5 years, who during recovery from a moderately severe attack of scarlet fever, developed a phlegmonous inflammation of the terminal ileum and cecum.

There was one case of acute duodenitis with multiple ulcerations in a woman of 66. An early peritonitis was present at operation.

There were fourteen patients, equally divided as to sex, who developed fatal peritonitis subsequent to lesions of the liver or gall bladder. These lesions were four cases of liver abscesses, one of which proved to be amebic; three of acute cholecystitis, two of which had perforated; three of empyema of the gall bladder; two of cirrhosis, and one case each of Pick's disease and subacute atrophy of the liver. A streptococcus was isolated from the peritoneal exudate of the latter.

Acute pancreatitis, either suppurative or hemorrhagic in character, incited a general peritonitis in two males and three females whose average age was 43 years. The oldest patient, a man of 70, had a carcinoma of the pancreas. In the others no previous disease was demonstrated and no causative factor for the pancreatitis was discovered.

OTHER ORGANS AND LESIONS

The clinical course of renal disease was terminated in eleven cases by signs and symptoms of general peritonitis. At necropsy general peritonitis of undetermined origin was discovered. The renal lesions were five cases of lipoid nephrosis, three of chronic glomerulo-nephritis, one of acute glomerulo-nephritis, and two of pyelo-nephritis. Bacteriologic studies on three cases of lipoid nephrosis revealed streptococcus in two and pneumococcus in the other, the latter also having a pneumococcic meningitis. The average age of the six men and five women was 31 years.

Occasionally an acute cystitis may be the forerunner of a fatal peritonitis. There were nine such instances, seven being in men. In four cases there was an acutely inflamed diverticulum of the bladder which had progressed to gangrene and perforation. In three cases without diverticula, there was a perforation of the wall of an acute gangrenous bladder. Two cases were associated with spinal cord lesions; namely, tabes dorsalis and a posterior lateral sclerosis of pernicous anemia.

A focus of suppurative inflammation in tissues adjacent to the

peritoneum may occasionally incite a peritonitis. In this series there were eight such cases, six being in males. The suppurative lesions were two cases of prostatic abscess, two of psoas abscess, (one associated with a general amyloidosis), two of perinephritic abscess, one perivesical abscess, and one of widespread retroperitoneal cellulitis. The average age of this group was 44.5 years.

A very interesting group of ten cases resulted from umbilical infection. There were seven males and three females, nine of whom were less than 3 weeks old. One case followed accidental detachment of the cord and two had liver abscesses.

A clinically primary intrathoracic disease was terminated by a general peritonitis in fifteen cases. The pathologic lesions disclosed at necropsy tended to show that the chest lesions were older than the peritoneal ones. There were eight cases of pneumonia, all except one of which were lobular in type. The intrathoracic lesion in the remaining seven cases was empyema. This condition was related to a previous pneumonia in most cases, but in one was associated with a pulmonary carcinoma. The average age of this group was 25 years.

GENERAL CONDITIONS

A terminal peritonitis developed in thirteen cases of pyemia or septicemia. The average age of the seven males and six females was 26 years, but four were under 6 months of age. The primary focus of infection was not found in five instances, though the findings were clinically and pathologically those of a septicemia. In the other eight cases a definite focus of infection was found, as crushing injury of the foot, cellulitis of leg, ulcerative vulvitis, hand injury, suppurative mastitis, ischiorectal abscess, knee joint suppuration, and suppuration about a Lane plate used for a non-united fracture of the femur.

Generalized purulent peritonitis complicated the course of fifteen cases of acute middle ear or mastoid inflammation. There were nine male and six female patients, eleven of whom were under 1 year of age. In ten instances the primary infective focus was in the middle ear, and in the remaining five, it was located

in the mastoid cells. At necropsy no intra-abdominal source of the peritonitis could be demonstrated, but one patient had received intraperitoneal medication, and it is possible that the infective agent was introduced by the procedure. Bacteriologic

TABLE 4

CLASSIFICATION OF THIRTY-SIX CASES OF PERITONITIS (UNIVERSITY OF MISSOURI SERIES)

TYPE OF CASE	NUMBER	PER CENT OF TOTAL	REMARKS
Post-operative	9	25.0	1 case each of mesenteric cyst; cancer prostate; sarcoma of liver; ectopic pregnancy; Caesarian section; paracentesis. Type of operation not ascertained in 3 cases
Acute appendicitis	5	14.0	No operation in 2
Perforated peptic ulcer	5	14.0	3 gastric, 2 duodenal. Operative repair in 4 cases
Post-abortion	3	8.3	Acute endometritis and salpingitis in all
Post-traumatic	3	8.3	2 had perforation of ileum; one from stab; other gunshot wound. No operation in either. One had perforated kidney. Operation
Tuberculous peritonitis	2	5.5	Both had active pulmonary lesions; one had caseous mesenteric nodes
Septicemia	2	5.5	Focus of infection: antrum in one; carbuncle of neck in other
Cancer of stomach	1	2.7	Male 54. No operation
Perforated typhoid ulcer	1	2.7	Perforation in ileum. Operative repair
Perforated tuberculous ulcer	1	2.7	Female 25. Ulceration of ileum
Incarcerated hernia	1	2.7	Male 61. Inguinal hernia. Gangrene of ileum
Phlegmonous gastritis	1	2.7	Male 70
Abdominal pregnancy	1	2.7	Age 33. Full term fetus
Congenital heart	1	2.7	Male 24. Ascites
Total	36		

studies were made on the peritoneal exudate of six cases and all revealed a pure culture of a streptococcus.

Acute pharyngitis diagnosed clinically as septic sore throat was the forerunner of a general purulent peritonitis in six cases,

four of which were females. The average age of the group was 9.5 years, but four were children under 1 year of age. The necropsy findings in these cases were a generalized peritonitis for which no intra-abdominal source could be demonstrated. Bacteriologic investigation of two cases revealed a streptococcus in one and a pneumococcus in the other

Erysipelas preceded a general peritonitis in seven patients, six being in females, and with one exception, all were less than 2 years of age. The skin lesion was facial in five cases, over the legs in one, and vulvar in one. Bacteriologic studies revealed a streptococcus in four cases so examined

Subacute bacterial endocarditis was terminated in two cases by peritonitis. One case was a women of 27. The other was a youth of 17, in whom septic infarction and inflammation of the spleen occurred prior to the general peritonitis.

It occurred to the author that a study of this problem based on an entirely different series of autopsies might be interesting and valuable. Accordingly, the records of the Department of Pathology of the University of Missouri were examined. The autopsy protocols for the period 1922 to 1934 numbered 294. The sex ratio was quite similar to that of the general necropsy series at Minnesota, since there were 192 male subjects to 102 females. There were thirty-six cases of peritonitis (12.2 per cent of all bodies examined) with a sex ratio of twenty-eight males to eight females. These cases, tabulated on the basis of etiology and arranged in order of frequency, are shown in table 4. It will be noted that while this is a small group of cases, the findings correspond quite well with those of the larger series

In relation to the systems of the body the 1000 cases may be grouped as follows:

Alimentary tract, 522 cases
Female reproductive system, 193
Hematogenous infection, 88
Accessory glands of digestion, 57
Urinary and male reproductive system, 52
Lesions in tissue adjacent to peritoneum, 33
Miscellaneous, as splenic lesion, exploratory operation, et cetera, 55

SUMMARY AND CONCLUSIONS

(1) This is a report of a study of 1000 cases of peritonitis diagnosed at necropsy.

(2) On adjustment of proportionate sexes under study, peritonitis was found twice as frequently in females as in males.

(3) The greatest number of cases for any decade occurred in the 20–30 year period

(4) Bacteriologic studies revealed streptococci as being the predominant organism, they being found in 75 per cent of the cases so studied.

(5) Tuberculosis was the cause of peritonitis in 100 cases, or 10 per cent.

(6) Post-abortive peritonitis was found in 77 cases, over 16 per cent of the female patients.

(7) The greatest number of cases of peritonitis had the origin of the disease in the gastro-intestinal tract.

(8) While no age group adapts itself to a single etiologic type of peritonitis, it was found possible to group the cases into three age periods where there were definite predominating factors:

(a) Infancy and early childhood, where peritonitis was secondary to otitis media, pharyngitis, erysipelas, and umbilical infections.

(b) Adults of the third and fourth decade, where the primary lesion was found especially in the appendix, female genital organs, and incident to trauma or tuberculosis.

(c) Late adulthood, where peritonitis was incident to perforated peptic ulcer, strangulated hernia, mesenteric thrombosis, malignant tumors, and inflammations of the male genito-urinary tract.

(9) The study of a small group of cases from an entirely different source revealed very similar findings.

Acknowledgment is hereby made to Dr. E. T. Bell, Director of the Department of Pathology of the University of Minnesota, for permission to use the material from his department.

REFERENCE

(1) Brines, O. A.: An analysis of 1535 autopsies. Am. Jour. Clin. Path., **2**: 37–55. 1932.

PAROXYSMAL "MARCH" HAEMOGLOBINURIA

With a Report of a Case

E. M. WATSON and L. C. FISCHER

From the Department of Medicine (Division of Pathological Chemistry), University of Western Ontario Medical School, London, Canada

The intravascular destruction of erythrocytes leading to hemoglobinemia and hemoglobinuria may be the result of a variety of causes such as have been outlined by Weir.[17] The most familiar type of hemoglobinuria, namely, paroxysmal hemoglobinuria, is regarded generally as a disease entity with rather characteristic clinical and immunological features. Since these have been reviewed comprehensively by Macalister,[7] Mackenzie[8] and Swineford,[16] further reiteration of the topic may appear an unnecessary repetition of accredited data. Yet it would seem pertinent for purposes of comparison to allude to some of the salient features of this disease.

True paroxysmal hemoglobinuria occurs in some syphilitics due to the development of an autohemolysin which under certain circumstances, especially following exposure to cold, is capable of effecting the destruction of erythrocytes with the consequent excretion of hemoglobin or some derivative of it, in the urine. As an accompaniment of this pathological process, the individual so affected frequently experiences chills and exhibits an elevation of temperature. Several factors other than cold, for example, exertion, fatigue and emotional stress, may at times act as exciting causes of the paroxysms. An etiological relationship between paroxysmal hemoglobinuria and syphilis is an established fact but the actual significance of the association is as yet undetermined. Mackenzie[8] states that the evidence seems to justify the conclusion that paroxysmal hemoglobinuria is usually, and perhaps always, a manifestation of syphilis and that in more than 90 per cent of cases the Wassermann reaction is positive. The

hemoglobinuria is frequently cured or relieved by anti-syphilitic treatment.

Valuable contributions to the subject comprise the demonstration by Eason[3] and by Donath and Landsteiner[2] of the existence of a specific hemolysin in the blood of paroxysmal hemoglobinurics. Their discoveries have supplied not only an explanation for the hemolysis but they have served also to provide a diagnostic aid in the form of the Donath-Landsteiner test which is said to be positive only in cases of true paroxysmal hemoglobinuria.

One phase of the hemolytic reaction which is peculiar to true paroxysmal hemoglobinuria is dependent upon a reduction of the temperature of the blood. Union of the lysin and the erythrocytes occurs only at a low temperature and with the subsequent warming of the cells lysis takes place. This explains the rôle of chilling in the causation of the attacks of hemoglobinemia and hemoglobinuria which may be promoted in predisposed individuals by submerging the hands or feet in cold water. Such phenomena constitute a rational basis for the Rosenbach test[13] and the Ehrlich test.[4]

As intimated above, exertion, with or without coincidental exposure to cold, may act as the exciting factor in the production of the paroxysms of hemoglobinuria in certain syphilitic subjects, as exemplified in the case reported by Connor.[1] But there is a variety of paroxysmal hemoglobinuria which may occur in non-syphilitics, the sole causative factor for which appears to be physical effort. This particular condition, heretofore observed principally in soldiers, has been described by certain German investigators as "die Marschhämoglobinurie." Walking or marching seems to be the important factor responsible for the onset of the symptoms of the disease which bears no relationship to syphilis, exposure to cold or to the presence of the autohemolysin of Donath and Landsteiner. Other forms of bodily exertion, such as cycling, do not appear to be as effective in the production of the condition as is walking. A description of the disorder together with a discussion of some of the earlier observations concerning it have been supplied by Meyer.[10] A recent case has been reported by Lang and Braun.[6]

Apart from the data supplied in the German literature, little if any, information is available regarding the so-called march hemoglobinuria. Apparently not any cases have been reported in the literature published in the English language with the exception, perhaps, of the three cases of hemoglobinuria in soldiers described by MacManus.[9] In view of the relative obscurity of the condition some observations concerning a case which presents the manifestations of march hemoglobinuria are recorded below.

CASE REPORT

A man, aged thirty-six, was admitted to the Victoria Hospital on March 20th, 1934, complaining of abdominal pain and the passage of dark coloured urine. A preliminary examination revealed that the patient was not acutely ill. There was no rigidity of the abdominal wall and no areas of localized tenderness could be elicited. Neither was there any urinary distress. The heart and lungs were not abnormal. The temperature was 99°F.; the pulse 68 and the respirations 20 per minute. The hemoglobin was 95 per cent (Dare); erythrocytes, 5,170,000; colour index, 0.92; leukocytes, 11,450, with the following differential formula: neutrophiles, 63 per cent (mature forms, 46 per cent, young forms, 17 per cent), lymphocytes, 29 per cent, eosinophiles, 3 per cent and monocytes, 5 per cent. The reticulocytes were 0.6 per cent. The urine, which was a deep red colour and slightly cloudy, gave a marked reaction for albumin but did not contain sugar. Microscopic examination of the centrifuged deposit showed an occasional erythrocyte, but no pus cells or casts were observed. On spectroscopic examination of the urine, pronounced absorption bands corresponding in position to those caused by oxyhemoglobin were seen. The serum obtained from a sample of venous blood was red due to a pigment which was identified as oxyhemoglobin. The urine passed on the following day presented a normal appearance; it did not contain any protein, blood pigment or blood cells. The subjective symptoms in the meantime had disappeared and the temperature was normal. A diagnosis of hemoglobinemia and hemoglobinuria was made and a more detailed study of the patient was undertaken.

This man, who was born the third child of a family of nine, has lived always in Ontario. His early years were uneventful from the medical point of view and the family history was irrelevant. At the age of 26 he suffered bilateral pneumonia and three years later he was under observation in a hospital for pulmonary diseases but a diagnosis of tuberculosis was not established. Careful questioning failed to gain an acknowledgment of venereal infection or malaria.

He had worked as a labourer at various occupations but since 1930, being unemployed, he has wandered about from place to place living the life of a transient. In 1928 and afterwards, he suffered occasionally from cramp-like abdominal pains. X-ray examination of the gastrointestinal tract in October,

1927, showed no evidence of gastric or duodenal ulcer. Gastroptosis and enteroptosis were present, however, with a slightly delayed emptying time of the stomach; 20 per cent of the barium remained in the stomach after eight hours. In December 1932 he noticed for the first time that his urine was red and that after a short time it was again a natural colour. The passage of dark or red urine has occurred at irregular intervals since that date. Experience has led him to relate its occurrence to physical exertion in the form of walking. He observed that a continuous walk of from 5 to 15 miles or repeated walks of shorter distances would precipitate the attacks which were preceded usually by cramp-like abdominal pains and a feeling of malaise. When he was fortunate enough to pursue his journeys by some mode of transit other than on foot or if he remained quiet in one place he was entirely free from the symptoms. The condition did not present any seasonal or climatic characteristics and there was no reason to implicate the toxic action of drugs, chemicals or any hemolytic poison in its causation.

A more complete physical exmination revealed nothing remarkable. The man was of slender build but well nourished and presented a rather swarthy appearance. There was no obvious jaundice and nothing was found to arouse a suspicion of syphilis. The spleen and liver were not enlarged. The laboratory findings except during the paroxysms of hemoglobinuria, or as a result of other circumstances as noted below, were essentially normal. Repeated Wassermann and Kahn tests on the blood serum were negative. The intravenous injection of a provocative dose of arsphenamine failed to produce a positive Wassermann reaction. Wassermann tests on the spinal fluids were negative also. The resistance of the erythrocytes to hypotonic salt solution was normal. Studies of the coagulability of the blood yielded normal results. Two days after an attack of hemoglobinuria the icterus index was 4.0, the qualitative van den Bergh reaction was normal and the serum bilirubin 0.2 mgm. per cent. An extensive investigation of the kidney functions showed no abnormality. The Donath-Landsteiner test for the presence in the blood of an autohemolysin, carried out according to the technique described by Sanford[14] was persistently negative. Likewise, this test on the spinal fluid was negative. The basal metabolic rate was minus 10 per cent. The blood chemical findings were: non-protein nitrogen, 28.5; creatinine, 1.2; sugar, 76; calcium, 10.3; phosphorus, 5.2 and cholesterol 130 mgm. per cent. No anemia was demonstrated but blood smears made during the attacks of hemoglobinuria showed the presence of poikilocytes; some of the erythrocytes possessed a "four-leaf clover" appearance. During the inter-paroxysmal periods the erythrocytes presented uniform outlines.

Various attempts were made to induce attacks of hemoglobinuria in this patient, as by immersing the hands or feet in ice-water (Rosenbach test), increasing the metabolic processes artificially and by walking. The last procedure was the only effective means of producing the phenomenon.

In view of the well-known etiological relationship of true paroxysmal hemoglobinuria to exposure to cold and the fact that the initial attack of hemo-

globinuria experienced by this patient occurred during the month of December, the chilling or Rosenbach test was carried out several times. Once, when the feet and lower part of the legs had been immersed in ice-cold water for 30 minutes, a definite trace of albumin could be detected in the urine which was voided one and one-half hours later. But similar tests failed to produce albuminuria and on no occasion was hemoglobinuria or a suggestion of it produced by exposure to cold after the manner indicated.

Having been kept in bed under observation for several days, the patient was allowed to be up and about the ward. He then complained of intermittent abdominal pains which subsided, as a rule, when he would lie down, but he did experience them occasionally at night while in bed. No hemoglobinuria occurred during this régime but small amounts of albumin appeared in the mixed 24-hour urine on two days.

The patient was then started on a series of walks outside the hospital. On the afternoon of April 3rd he walked between two and three miles. The same distance was travelled on the next morning. During the afternoon of that day he experienced abdominal distress and felt that an attack of "colour" was coming on, but no alteration of the appearance of the urine was noted. The 24-hour urine for April 3rd contained, however, a slight amount of albumin and an occasional erythrocyte. He remained in bed on the 5th on account of feeling indisposed. On the afternoon of the 6th, he walked three miles and during the morning of the 7th he repeated the performance. It should be noted that the weather on these days was not cold or chilly. As a matter of fact, the atmospheric conditions were mild and pleasant. About 2.00 p.m. on April 7th, the urine was noticed to be a light reddish colour. Samples passed at frequent intervals revealed a gradual darkening of the urine; the maximum discoloration, a deep red, being attained about 5.00 p.m. By 10.00 p.m. the urine was again normal in appearance. A sample of blood withdrawn from a vein at 4.30 p.m. provided serum which was a bright red colour due to oxyhemoglobin. Another sample of blood obtained the following morning yielded a pale yellowish serum.

Similar attacks of hemoglobinemia and hemoglobinuria could be brought about in this patient at any time by walking. Following one of them a spinal puncture was performed and the fluid was found to be normal in appearance and failed to give a positive test for hemoglobin. During an attack of hemoglobinuria, the total plasma proteins were 6.7 per cent and the albumin-globulin ratio 1.9. Coincidentally, the albumin-globulin ratio of the urine was 0.3. None of the paroxysms were accompanied by chills and the temperature did not rise above 99°F. during any of the attacks.

Relating the phenomenon of hemoglobinemia in this patient with a possible alteration of the general metabolism accompanying physical activity, observations were made in order to determine whether the abnormality could be produced by raising the body temperature or otherwise modifying the metabolic processes. Consequently, the man was given 2 grains of desiccated thyroid by mouth; he was wrapped in blankets and an electric pad was placed in his

bed. The oral temperature rose from 97.1°F. to 99.0°F. but no sign of hemoglobinuria was demonstrable. On another day, 25 million killed typhoid bacilli were injected intravenously. A pronounced general reaction followed. While the temperature remained in the neighborhood of 101°F. for more than 24 hours and the man felt miserable, no hemoglobinuria occurred. Moderate albuminuria and biliuria appeared, however.

There was no apparent relationship between the slightly increased lactic acid content of the blood following walking and the occurrence of the hemoglobinuria.

The man's condition occasioned him little discomfort and no actual disability. So, after a period of time spent in the hospital, he resumed his wanderings and has not been available for further study.

DISCUSSION

The diagnosis of paroxysmal march hemoglobinuria in this patient was based upon the fact that etiological factors with the sole exception of walking, were lacking. The condition as described differed from true paroxysmal hemoglobinuria in the absence of any evidence of syphilis; the failure to demonstrate the existence in the blood, by means of the Donath-Landsteiner test, of a hemolytic agent; the inability to reproduce the phenomenon artificially by means of exposure to cold and the absence of chills and fever during the attacks.

In all probability the cases of hemoglobinuria in soldiers reported by MacManus[9] were examples of march hemoglobinuria although such a possibility was not suggested by that author. The exciting cause of the condition in those cases was attributed to "exposure to cold coupled with considerable bodily exertion." While it was stated that "in none was there any admission of syphilitic taint, the Wassermann reaction was not done in any of the cases." One of the soldiers gave a history of having suffered from malaria. In none of them was the hemoglobinuria recurrent. Two of the three men, all of whom were in the early stages of their military training, experienced but a single attack. The third man had one relapse six weeks after the initial attack.

Theories have been propounded in explanation of march hemoglobinuria but actually nothing of a decisive nature is known regarding its mechanism of production. Exactly what physical or chemical phenomena are concerned in the process is a problem

awaiting solution. The disease would appear to be related in some way to a strange perversion of the physiological processes which accompany muscular activity. In this regard it is noteworthy that Feigl[5] observed that more than one-half of the twenty-seven men whom he examined after an army pack march of 35 kilometers showed, by spectroscopic and chemical methods, blood pigment in the serum and in the urine. Perhaps march hemoglobinuria is an exaggeration, exemplified in certain predisposed individuals, of a more or less naturally occurring phenomenon. The matter of vasomotor instability is a factor to be considered. The possible rôle of CO_2 as a hemolytic agent is an uncertain quantity as mentioned by Mackenzie.[8] It has been suggested that the important etiological factor in march hemoglobinuria is lordosis, thus implying a relationship to orthostatic albuminuria.[12,15] The evidence in favour of such an association is by no means conclusive, however. It seems not unreasonable to assume that the condition bears some relationship to the so-called paralytic hemoglobinuria which has been observed to occur in certain degenerative diseases of the muscles.[11] Pending further investigations, the true explanation of the etiology of the condition must remain in abeyance.

SUMMARY

Paroxysmal march hemoglobinuria, as described in the German literature is a variety of periodically occurring hemoglobinuria, secondary to hemoglobinemia, in which the sole etiological factor appears to be physical activity in the form of marching or walking. The condition is unrelated to syphilis or exposure to cold and the existence in the blood of a hemolysin has not been demonstrated. In these respects the disease differs from true paroxysmal hemoglobinuria. An example of so-called paroxysmal march hemoglobinuria is recorded.

REFERENCES

(1) Connor, W. H.: Paroxysmal hemoglobinuria, case report. U. S. Naval Med. Bull., **23:** 501–504. 1925.

(2) Donath, J., and Landsteiner, K.: Ueber paroxysmale Hämoglobinurie. Münch. med. Wochenschr., **51:** 1590–1593. 1904.

(3) Eason, J.: The pathology of paroxysmal hemoglobinuria. Jour. Path. and Bact., **11:** 167–202. 1906.

(4) Ehrlich, P.: Ueber paroxysmale Hämoglobinurie. Deutsch. med. Wochenschr., **7:** 224–226. 1881.

(5) Feigl, J.: Chemische Blutuntersuchungen an den Teilnehmern eines Armee-Gepäckmarsches. Teil I. Über Umsatz und Ausscheidung von Blutfarbstoff. Hämoglobinämie, Hämatinämie und Hämoglobinurie. Biochem. Zeitschr., **76:** 88–106. 1916.

(6) Lang, K., and Braun, A.: Untersuchungen über einen Fall von paroxysmaler Marschhämoglobinurie und Hämatinurie. Zeitschr. f. Klin. Med., **118:** 374–382. 1931.

(7) Macalister, G. H. K.: The pathology of paroxysmal hemoglobinuria, a critical review. Quart. Jour. Med., **2:** 368–395. 1908–1909.

(8) Mackenzie, G. M.: Paroxysmal hemoglobinuria, a review. Medicine, **8:** 159–191. 1929.

(9) MacManus, D.: Three cases of paroxysmal hemoglobinuria in soldiers. Brit. Med. Jour. **1:** 552. 1916.

(10) Meyer, E.: Die Marschhämoglobinurie, In A. Bethe and others: Handbuch der Normalen und Pathologischen Physiologie. Berlin: J. Springer, vol. 6 (1), p. 596, 1928.

(11) Meyer, E.: Die paralytische Hämoglobinurie, In A. Bethe and others: Handbuch der Normalen und Pathologischen Physiologie. Berlin: J. Springer, vol. 6 (1), p. 598, 1928.

(12) Porges, O., and Strisower, R.: Offizielles Protokoll der k. k. Gesellschaft der Aerzte in Wien. Wien. klin. Wochenschr., **26:** 193–194. 1913.

(13) Rosenbach, O.: Beitrag zur Lehre von der periodischen Hämoglobinurie. Berlin. klin. Wochenschr., **17:** 132–134, 151–153. 1880.

(14) Sanford, A. H.: (Discussion of Dr. Weir's paper). Proc. Staff Meetings Mayo Clinic, **8:** 115–116. 1933.

(15) Schellong, F.: Untersuchungen über Marschhämoglobinurie; ihre Beziehung zur Kaltehämoglobinurie und orthostatischen albuminurie. Zeitschr. f. d. ges. exp. Med., **34:** 82–86. 1923.

(16) Swineford, O.: Paroxysmal hemoglobinuria, with report of a case. Jour. Lab. and Clin. Med., **16:** 347–353. 1931.

(17) Weir, J. F.: Recurring acute hemolytic crisis with hemoglobinuria. Proc. Staff Meetings Mayo Clinic, **8:** 110–116. 1933.

A VERY RAPID FLOCCULATION METHOD FOR THE DIAGNOSIS OF SYPHILIS

A Preliminary Report

F. RYTZ

From the Clinical Laboratories of the Minneapolis General Hospital, Minneapolis, Minnesota

The following flocculation method for the diagnosis of syphilis can be carried out in fifteen minutes including the coagulation of the blood. It is known thus far as M.G.H.P. (Minneapolis General Hospital Precipitation).

Fifty-three hundred and fifty tests by this method have been compared with Wassermann and Kahn reactions on the same serums, with the result that the method appears to be more reliable and more sensitive than the Kahn test as performed in this laboratory. Exact comparative data will be reported later.

Four factors account for both rapidity and sensitiveness: (1) artificial coagulation of the blood; (2) heating of the serum for three minutes only; (3) sensitization of the serum by means of ammonium sulphate; (4) use of an antigen emulsion so stable that it may be regarded as a "stock" reagent, available for immediate use without further manipulation.

Blood may be fully coagulated in from two to three minutes by placing the tube containing the blood in a water bath at 60 degrees C., at the same time stirring slowly with an applicator for one or two minutes. Clear serum can then be obtained after three minutes centrifugation at high speed.

The antigen found to be adjustable to this method is prepared as described by Noguchi,[2] except for the following modifications: Instead of 25 or 50 grams of dried heart muscle treated with alcohol, 100 grams of "Difco" beef heart powder are suspended in 500 cc. of absolute (ethyl) alcohol and shaken for two hours. The final antigen wax is dissolved in absolute (ethyl) alcohol in

the proportion of 1 gram of wax to 10 cc. of the alcohol. (Noguchi's method requires 0.3 gram of wax to 1 cc. of either and 9 cc. of methyl alcohol.) The wax is dissolved by shaking in a glass stoppered bottle and placing in a water bath at 55°C. for fifteen minutes. If the antigen is cloudy after standing in room temperature for 24 hours, it should be filtered until clear. It will then remain reliable for two months at room temperature.

The antigen emulsion is prepared essentially as described by Kline[1] except for the following modifications: 1 cc. of 1 per cent cholesterol in absolute alcohol is added to 0.8 cc. of 0.45 per cent of saline. The final quantity of 0.9 per cent saline added is 2.5 cc. (Kline's method requires the addition of 1 cc. of 1 per cent cholesterol suspended in 0.85 cc. of distilled water, and the final addition of 0.9 per cent saline is 2.45 cc.) As modified for this method the antigen emulsion is not heated before use as Kline recommends. It is reliable for a week at room temperature.

The amount of antigen required for the above quantity of emulsion is determined by simple quantitative serological titration, beginning with 0.05 cc. of antigen and ending with 0.25 cc., employing a known negative, a weakly positive, and a strongly positive serum, and using the same technique as for the test proper. The tubes showing the largest clumps of flocculation in the positive serums indicate the quantity of antigen to be added before final addition of 2.5 cc. of 0.9 per cent saline.

THE TEST

The test requires only one tube for each serum.

Place 0.15 cc. of serum in a tube 75 mm. long and 10 mm. (inside diameter).

Heat the serum in a water bath at 60 degrees C. for three minutes.

Remove from the bath and add 0.05 cc. of half saturated ammonium sulphate. Mix by shaking.

Add 0.05 cc. of antigen emulsion. Mix by shaking. Add 1 cc. of 0.9 per cent saline and rotate in such a manner that the antigen particles become evenly distributed.

Shake in the Kahn shaker for three minutes, or by hand in such a manner that the rack, in even back and forth movements, makes about 275 movements per minute.

Add 2.0 cc. of 0.9 per cent saline and invert the tube slowly two or three times just before reading. It is important not to shake the tube at this time.

In order not to miss a 1 plus reaction, the results are preferably read over the Fisher Lamp for reading Kahns, aided by a hand lens. The slanted part of the contents of the tube should be relied upon for estimating the results.

A 1 plus reaction consists of very tiny, densely scattered flocculation particles in a slightly opalescent fluid. Two, 3 and 4 plus reactions show clumps of flocculation in a clear fluid, the clumps varying in size according to the positiveness of the serum.

A negative test shows minute antigen particles only, in a slightly hazy fluid without clumping.

SPINAL FLUID

Apparently reliable results may be obtained with spinal fluid in about eight minutes.

Method: To 0.5 cc. of unheated fluid add 0.1 cc. of half saturated ammonium sulphate and mix. Add 0.05 cc. of antigen emulsion and again mix. Shake for five minutes. Add 2.5 cc. of 0.9 cc. saline. Invert once or twice and read.

REFERENCES

(1) KLINE: In KOLMER AND BAERNER: Approved laboratory technic. New York: D. Appleton & Co. P. 498. 1931.

(2) NOGUCHI: In TODD AND SANFORD: Clinical diagnosis by laboratory methods. Philadelphia: W. B. Saunders Co. P. 609. 1931.

STUDIES IN CEREBRO-SPINAL FLUID. II

BENJAMIN GRUSKIN

Department of Oncology and Experimental Pathology, Temple University, School of Medicine, Philadelphia

In a previous paper,[1] a test was described for the differentiation of spinal fluids by means of a starch-iodine solution. The test was based on the fact that the proteins which are increased in the spinal fluid in pathological conditions have the power of absorbing iodine from its combination with starch, causing the blue color of the solution to disappear. Using a definite dilution of spinal fluid and starch-iodine solution, characteristic curves were obtained in each case for normal fluids, those of tabes dorsalis, paresis, or meningitis.

In recent studies made on spinal fluids, a comparison of results has been made using the starch and iodine solution on one series, and on another using glycogen with iodine. It was found that the same phenomena occurred in each series, that is, the same number of tubes were attacked. Instead of the blue color of the starch-iodine reaction, the glycogen and iodine gave the characteristic color of port wine, and this color gradually faded out in the dilution, as does the blue color of the starch-iodine.

The starch-iodine reaction and the glycogen-iodine reaction were run simultaneously on spinal fluids from sixty cases, including normal, tabetic, paretic, meningococcic meningitis, tuberculous meningitis, and a few brain tumor cases. In each case the reaction of the two solutions was proportionally similar, and in most was identical in the degree of change.

While materially the results obtained with glycogen do not differ from those obtained with starch, the fact that the same number of tubes were attacked by using glycogen as when starch was used, as well as the value of checking the one by the other for correct results, justifies the reporting of the experiment. Mention must be made that the iodine solution employed with the

glycogen is made up differently from that used in the starch-iodine reaction. It was necessary to use a stronger solution to obtain results more easily read. The solutions used were as follows:

Glycogen.....1 per cent solution in distilled water
Iodine solution.....1 gram iodine, 2 grams potassium iodide, in 100 cc. distilled water

It is interesting that the phenomena displayed by the starch reaction are also present in the glycogen reaction. For example, the presence of a pellicle in the spinal fluid shortens the length of the curve in the starch-iodide reaction and also shortens the curve in the glycogen reaction.

The principal advantage of the glycogen over the starch might be the fact that it is more consistent in reaction than the starch, for in our experience we have found that the various soluble starches of the different manufacturers are not equal in reaction. The disadvantages of using glycogen must, however, be taken into consideration; first, the expense involved; secondly, the reaction being somewhat harder to read (until one becomes very familiar with it by constant use); third, the shorter duration of the glycogen reaction.

CONCLUSIONS

Using the method described[1] for a spinal fluid test for differentiating various diseases affecting the cord and the meninges, experimental work has been carried out on the method, using various starches, and glycogen in place of starch. It has been observed, in a long series of cases, that starches of different manufacture vary in the degree of the reaction when combined with the usual amount of iodine and added to spinal fluids in the method of the test. Glycogen used in place of starch has given the same characteristic curves for tabes, paresis, and meningitis, and normal reactions. The glycogen was found to be more stable in reaction, but has the disadvantage of being expensive for ordinary use, gives a color reaction more difficult to observe than the blue

of the starch iodine, and gives a reaction of shorter duration than the starch-iodine method.

REFERENCE

(1) GRUSKIN, B.: Studies in cerebrospinal fluid. I. Am. Jour. Clin. Path., **1**: 441–447. 1931.

TECHNIC FOR PRESERVATION AND MICROSCOPIC DEMONSTRATION OF NODULES IN GOUT

ELENA DE GALANTHA

Pathology Laboratory, The Mayo Clinic, Rochester, Minnesota

(1) Fix fresh material immediately in absolute alcohol. Two changes of four hours each for thin specimens; longer (to 24 hours) for thicker specimens.

(2) Xylol paraffin (equal parts xylol and parawax) kept at 57°C. for two hours.

(3) Hard paraffin (melting point 56°) for one hour and embed.

(4) Cut sections about 8 microns thick, fix to slide and dry in oven at 37°C. for two hours.

(5) Remove paraffin with xylol and then wash in absolute alcohol.

(6) Stain 3 minutes in Harris hematoxylin.

(7) Wash in absolute alcohol and counterstain with 2 per cent alcoholic eosin one minute.

(8) Clear in several changes absolute alcohol, carbol xylol and xylol.

(9) Mount in xylol Canada balsam.

For specific demonstration of urate crystals, use above technic through stage 5, then

(6A) Place slides in 20 per cent silver nitrate solution and expose to strong sunlight until the urates are a bright rose color (one to four hours).

(7A) Prepare solution of (a) 10 cc. 3 per cent gelatin in hot water; (b) 3 cc. 20 per cent silver nitrate and (c) 2 cc. 2 per cent hydrochinon, and pour this over slides until the urates turn black and the connective tissues are yellow.

(8A) Wash quickly in hot water (57°C.).

(9A) Clear in absolute alcohol and xylol as in stage 8 above.

(10A) Mount in xylol Canada balsam.

For decalcifying specimens containing bone:

(1) Place thin specimens in absolute alcohol containing 2 per cent concentrated nitric acid. Change to fresh solution every 24 hours, until the bone is softened.

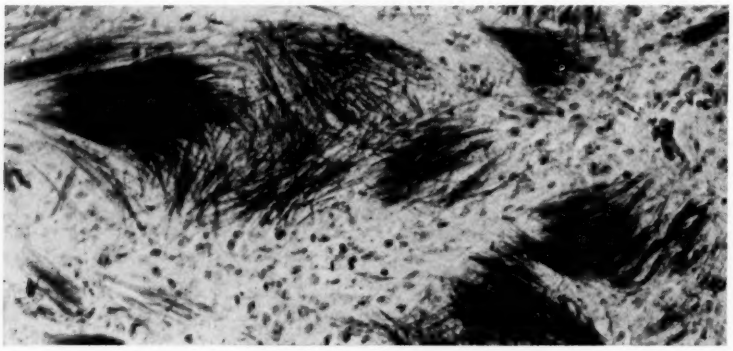


FIG. 1. KNEE JOINT CAPSULE

Stained by the silver method to show urate crystals

(2) Wash in several changes of absolute alcohol for 24 hours.

(3) Embed and handle as above.

EDITORIAL

The Present Status of BCG (Bacillus Calmette-Guerin) Vaccination and the Clinical Pathologist

Almost a decade has elapsed since the initiation of one of the most extensive human experiments ever performed and still there exists an indecision particularly evident among English speaking races regarding the safety of this procedure and its feasibility. The average American physician expresses a fear, probably justified by certain evidence noted in the English scientific literature, against BCG vaccination* because viable tubercle bacilli though "avirulent" have been stamped as possessing potential "virulent" dangers which are not clearly defined by inadequate and not easily repeated experiments. These experiments vary in the descriptions given by different students supporting the cause for alarm. Yet the human experiment extensively carried on in Romance Countries and emanating from France, the birthplace of Pasteurian vaccination, would hardly warrant such extreme caution. In France alone, over 200,000 children were treated per os before 1930. With the acknowledged guilt for the Lübeck disaster placed elsewhere after a thorough and painstaking investigation, human tests in various parts of the world, including several series in the United States and England, have resulted in no outstanding proved disaster attributable to BCG, although there are those skeptics who still expect a wholsesale outbreak in future years due to some hidden "virulent" propensities of the bovine "avirulent" bacilli. Until sufficient evidence accumulates

* "BCG" is the abbreviation for Bacillus Calmette-Guerin, an attenuated bovine tubercle bacillus described by Drs. Calmette and Guerin of Pasteur Institute who maintain that the culture was originally one of "virulent" bovine tubercle bacilli which has been attenuated by about fifteen years of artificial cultivation on a nutrient medium of glycerol, bile, and potato devised by them for this purpose.

from various different experimental sources to verify or disprove the views of the Petroff and Medlar schools, who contend that the apparently "avirulent" culture of BCG contains, besides the predominating rough "avirulent" bovine tubercle bacilli, also potential smooth "virulent" bovine tubercle bacilli, or that the rough "avirulent" bovine tubercle bacilli readily transform under suitable conditions of nutrient mediums or in in vivo surroundings into the "virulent" smooth forms, indecision will prevail and with some justification.

It is possible that the clinical pathologist will yet have to render intelligent aid to his medical confreres in both an experimental and educational capacity. If BCG contains virulent potentialities, it should be possible to outline the technic for obtaining these so that any clinical pathologist may verify such properties and soon bring to light the true relation of facts. Further, the autopsy room also possesses the secret to the potential disastrous possibilities, if they exist. Thus, from vaccination to postmortem, especially accessible to the clinical pathologist, data should in time yield the answer to this important question.

Regarding the value of BCG vaccination, the concensus of scientific evidence accumulated from Koch's pioneer studies to date, indicate an unquestioned value of the presence of tubercle bacilli in the body, and this property is preserved in the avirulent culture of BCG although the efficacy of enteral introduction as first advocated by Calmette may with justice be questioned. It also appears that killed bacilli have lost the desired properties essential to successful vaccination. It would seem rather simple from an experimental standpoint and with appropriately used controls, especially for virulence tests, to verify the contention that an avirulent culture of BCG contains virulent bacilli. Nutrient culture methods are now available which are capable of adequately growing both virulent human or bovine tubercle bacilli and avirulent tubercle bacilli. It should also be possible to reverse the phenomenon again and by appropriate use of culture mediums to transform the virulent strains, if the medium is the deciding factor, to avirulent strains. Up to the present there is no authentic method available for producing avirulent bacilli

from virulent human or bovine bacilli within a reasonably short period of time. Those who have accurately studied this problem have been unable to outline a method; and the transformation has only occurred naturally slowly and over years of artificial cultivation. It is even questioned, and justifiably so, whether the avirulence of BCG was not attained as a natural slow process of artificial cultivation of a decade and a half by Calmette and Guerin, rather than through the use of the glycerol-bile-potato medium. Until the transformation methods from virulence to avirulence and vice versa can be outlined accurately and can be duplicated by the majority of qualified students, the adherents of BCG may with some justice contend that, within reasonable limits, BCG administered to normal non-tuberculous individuals, serves, not as an absolute protection against tuberculosis, but to endow the individual with a relative protection only at present obtainable with viable bacilli. Adherents to this view prefer BCG, since its guilt as a disease producer requires further verification before accepting condemnation and discontinuing the method. Park, on the basis of both animal and numerous human trials, would appear to favor the view of its harmlessness. Whether wholesale general vaccination as carried out in Europe is justified would appear to be a matter of cautious judgment, and it seems better until all aspects of the virulence problem have been settled to urge its use only in the presence of uncontrollable and evident tuberculous hazard, which is still prevalent enough. The mode of introduction and size of dose when used is pertinent as a protection against possible disaster from the presence of potential virulent bacilli, if such exist at all. In experiments with virulent bacilli, where this can be tested, intracutaneous introduction offers a thousand-fold greater protection against possible spread than subcutaneous or other internal routes, and smaller doses guarantee destruction of the bacilli within reasonable time up to a year or so at the site of inoculation, as compared with too prolonged persistence with excessive doses leading to too much local tissue destruction and caseation.

It is hoped that the clinical pathologist will assist in establishing

the stability of BCG and thus place its use on a reliable basis or point out definitely the inherent dangers that exist in its use. Only time and conscientious controlled experimental tests will permanently establish the value and safety of BCG or relegate it to the archives of trials that failed because crucial value was overbalanced by inherent evident dangers. Or possibly, it will open the avenue to newer, better, and safer methods of approach to an important, unsolved problem in medicine.*

* A good review of the voluminous literature accumulated on BCG may be gleaned from the following four articles:

(1) Park, W. H., Kereszturi, Camille, and Mishulow, Lucy: Effect of vaccination with BCG on children from tuberculous families. Jour. Am. Med. Assn., **101:** 1619–1625. 1933.

(2) Tiedemann, H. J.: Sammelreferat über das Englisch-sprachige BCG-Schrifttum. Zentralbl. f. d. ges. Tuberk.-Forsch., **33:** 135–144. 1930.

(3) Tiedemann, H. J.: Kritisches Sammelreferat über das neue Englisch-sprachige BCG-Schrifttum. Zentralbl. f. d. ges. Tuberk.-forsch., **39:** 433–450. 1933.

(4) Weleminsky, F.: Die BCG-Literatur in französischer Sprache. Zentralbl. f. d. gesam. Tuberk.-forsch., **33:** 129–135. 1930.

NEWS AND NOTICES

The following Committees have been appointed: *Committee on Life Membership*, O. B. Hunter, *Chairman*, and R. C. Beck; *Commercial Exhibits*, A. W. Freshman, *Chairman*, P. Hillkowitz, and A. S. Giordano.

Attention of pathologists is called to the Third International Congress of Comparative Pathology to be held in Athens, Greece, April 15 to April 18, 1936. The subjects on which special reports will be made are as follows: nephrosis and amyloidosis, echinococcosis, leishmaniasis, spirochetosis, avitaminosis, echinococcosis in the domestic animals, spirochetosis in animals, anaerobic infections in the domestic animals, leishmaniasis in animals, and immunity in vegetables. In addition, a cruise of twelve days in Greece will allow members to follow this interesting program which will be given in various cities.

Members of the Society desiring to present papers at the Atlantic City meeting of the Society should send their titles and requests for space on the program to the Secretary of the Society as soon as possible. Attention of members is called to the fact that papers presented at the meeting are the property of the Society and must not be submitted for publication to other Journals than the American Journal of Clinical Pathology. Reservations for rooms should be sent directly to the Manager, Hotel Madison, Atlantic City, N. J. The Secretary will shortly mail to each member a certificate entitling him to reduced railroad fare. The fare will amount to one and one-third fare per round trip with the privilege of returning by a different route if desired and a time limit of thirty days from the time of issuance. This special rate applies not only to members but to those of the immediate family.

Attention of Society members is called to the new catalog issued by the Kimball Glass Company which describes the manufacture of their blue line glass ware which is sold by biological supply houses advertising in this JOURNAL. The Kimball Glass Company has been a supporter of this JOURNAL for a number of years and enjoys the confidence of the members of the Society.